TAYADE, AMITKUMAR GULABRAO, Ph.D. Role of Medial Olivocochlear Neural Efferent Pathway in Perception of Tinnitus in Presence of Silence. (2018)
Directed by Dr. Denise Tucker. 116 pp.

Over 20 million Americans struggle with troublesome effects of tinnitus. Tinnitus has a negative impact on a patient's overall health and social well-being. Tinnitus can be a disabling condition. People with tinnitus regularly experience distress, depression, anxiety, sleep disturbances, frustration, poor concentration and in some cases pain. Currently, there are no scientifically validated cures available for most types of tinnitus. In fact, there is a deficiency in neurophysiological knowledge related to tinnitus. There is an informational gap between silence, which exacerbate or trigger tinnitus and Medial Oliovocochlear (MOC) efferent neural pathway connection. The primary aim of this study is to investigate the MOC efferent neural pathway and neural connections responsible for tinnitus generation in silence/sensory deprivation. The primary hypothesis of this study is that silence/sensory deprivation makes MOC efferent neural pathway hyperactive which participate in tinnitus perception.

Method: fifty-eight normal hearing individuals between age 18-35 years were recruited as participants in this study. By placing normal hearing participants in a sound booth for 10 minutes, silence/sensory deprivation was created. This offered assessment of MOC neural pathway in normal hearing participants in silence. Hyperactivity of MOC neural pathway was assessed by its more suppressive effect on stimulated otoacoustic emissions (TEOAEs) in silence. The required auditory measurements were recorded in

the sound booth using recommended diagnostic protocols to ensure the effect of "only silence" on auditory structures.

Results: 41.4% of the participants perceived some type of tinnitus during/after 10 minutes of silence. Overall, Ringing was the most common type of tinnitus sound perception most participants who perceive tinnitus followed by "Cricket" and "Buzzing" sound. "Pulsating" or "Clear tone" sounds were less frequent followed by "Hissing," "Ocean Roar," and "Transformer." No statistically significant difference was found in the total TEOAE and TEOAE suppression amplitude before and after 10 minutes of silence. Post silence total TEOAE suppression between tinnitus perceiving and non-perceiving tinnitus was not statistically significantly different.

Conclusion: TEOAE generation is a peripheral phenomenon. Because tinnitus perception did not significantly change total TEOAE amplitude, the results may indicate higher central auditory structures as a source of tinnitus generation. Therefore, the results of the study support the notion that tinnitus is the central auditory processing phenomenon. The study may have failed to detect the changes in the medial olivocochlear efferent pathway because TEOAE tests might not be sensitive enough to detect the post silence changes in the pathway or top-down influence of the corticofugal pathway on lower auditory brainstem structures. This does not mean that medial olivocochlear efferent pathway does not participate in tinnitus perception. Results of the present study also seem to indicate that race may place a function in the perception of silence induced temporary tinnitus. Further investigation is needed to evaluate the

functional contribution of the medial olivocochlear efferent pathway in tinnitus perception.

ROLE OF MEDIAL OLIVOCOCHLEAR NEURAL EFFERENT PATHWAY IN PERCEPTION OF TINNITUS IN PRESENCE OF SILENCE

by

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A Dissertation Submitted to
the Faculty of The Graduate School at
The University of North Carolina at Greensboro
in Partial Fulfillment
of the Requirements for the Degree
Doctor of Philosophy

Greensboro
2018

Approved by

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APPROVAL PAGE

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ACKNOWLEDGMENTS

I would like to express the deep gratitude to Denise Tucker for her valuable guidance and support. I would like to extend my gratitude to my committee members, Lisa Fox-Thomas, George Michel, and Kristine Lundgren for their excellent support throughout my graduate program. I would like to thank my guide and mentor Kalyani Mandke for her valuable guidance. My special thanks go to all my friends Ishan, Carrie, Nilesh, Mohsin, Holly, Fadi, Cathrine, Ronda, and my entire cricket buddies for making my Ph.D. Journey memorable and enjoyable. I acknowledge with the deep feeling of respect, my gratitude towards my mother and family members, who have always been an immense source of encouragement and confidence throughout my life.

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CHAPTER I

INTRODUCTION

Tinnitus is the perception of sound in the absence of an external auditory stimulus (Møller, 2007). According to the American Tinnitus Association (ATA, 2017), an estimated 50 million people in the United States (16%) experience some form of tinnitus. Approximately 20 million people (6%) struggle with chronic tinnitus, while two million (< 1%) are completely disabled from it (data collected and analyzed from the 2011-2012 National Health and Nutrition Examination Survey conducted by the U.S. Centers for Disease Control). The results from neuroscience studies in tinnitus generally support the hypothesis that tinnitus is a central auditory processing disorder (Eggermont, 2012).

Currently, there is no medical cure for tinnitus. To identify a cure, researchers have examined the physiology of the auditory system of model animals. In such tinnitus studies, increased spontaneous firing rate (hyperactivity) in auditory neural structures such as auditory nerve fibers (Yang et al., 2007) and the dorsal cochlear nucleus (Finlyayson & Kaltenbatch, 2009) have been observed to result from cochlear damage. Thus, lack of sensory input because of peripheral hearing loss alters neural organization in the auditory pathway and results in rapid seemingly irreversible changes in the auditory system (Cook, Hung, Miller, Smith, & Tucci, 2002; Pasic & Rubel, 1991; Salvi, Wang, & Ding, 2000; Tucci, Cant, & Durham, 2001). Therefore, tinnitus seems to be

associated with less neural excitation in the periphery of the ascending auditory pathway and greater activity in more central auditory structures (Eggermont, 2012).

One part of the auditory pathway that might contribute to the perception of tinnitus is the efferent auditory pathway. This pathway is part of the descending central auditory pathway, which starts in the auditory cortex and terminates in the cochlea (Guinan, 2006). One part of the efferent auditory pathway, the olivocochlear bundle (OCB) is located within the brainstem and terminates inside the cochlea (Guinan, 2006). The olivocochlear bundle is divided into medial and lateral olivocochlear fibers. The thick, myelinated medial olivocochlear fibers project predominantly to the contralateral cochlea and terminate at the base of the outer hair cells (OHC) (Guinan, 2006). Most of the studies on olivocochlear neurons focus on medial olivocochlear fibers because of the ease with which it can be stimulated electrically and acoustically (Dhar & Hall, 2012). Upon activation, the medial olivocochlear fibers inhibit the outer hair cell activity resulting in decreased (suppressed) otoacoustic emission levels.

Otoacoustic emissions (OAEs) are the echo of sounds generated within the cochlea produced by the movement of the outer hair cell in response to a stimulus (Kemp, 2002). Medial olivocochlear fibers function can be assessed through suppression of otoacoustic emissions, in which white noise is presented to the opposite ear (contralateral, non-test ear) and variation in otoacoustic emission levels is observed in the ipsilateral (test) ear. Thus, OAEs might be used to as means to evaluate the differences in the efferent system function in patients with tinnitus. Suppression of otoacoustic emissions indicates the inhibitory influence of medial olivocochlear fibers on cochlear

amplification, which in turn reduces the auditory input to the ascending auditory pathway. Therefore, hyperactivity in the efferent medial olivocochlear fibers would, in turn, cause a distinctive reduction in cochlear amplification. Such reduction in cochlear amplification may cause less neural excitation in the periphery of the ascending auditory pathway. This operates similarly to sensory deprivation and could results in greater activity in more central auditory ascending and processing structures leading to the perception of tinnitus.

Several studies in patients with tinnitus and normal hearing have reported that there was no suppression effect on TEOAEs (transient otoacoustic emissions) in the frequency region of tinnitus, suggesting a medial olivocochlear fiber dysfunction (Chéry-Croze, Collet, & Morgon, 1993). The lack of transient otoacoustic emission suppression in patients with tinnitus and normal hearing has been confirmed (Lalaki et al., 2011; Paglialonga, Del Bo, Ravazzani, & Tognola, 2010). Thus, tinnitus has been related to both silence and medial olivocochlear pathway dysfunction.

Tinnitus Retraining Therapy (TRT), which includes directive counseling, use of sound therapy, and audiological testing, is an effective tinnitus management program (Jastreboff, 2000). In TRT, patients with tinnitus are often advised to avoid *silence*. When placed in silence for a short period of time, many normal hearing individuals perceive tinnitus (Heller & Bergman, 1953; Tucker et al., 2005). Thus, lack of auditory input can trigger or aggravate the perception of tinnitus perhaps via alteration in the function of central auditory neural pathways. The assessment of medial olivocochlear pathway in normally hearing subjects without tinnitus, who perceive tinnitus when placed in silence,

may reveal the role of the efferent systems in tinnitus perception. Moreover, such manipulations may reveal an effect of silence/sensory deprivation on medial olivocochlear efferent function.

The purpose of this study is to assess the role of the efferent auditory pathway (medial olivocochlear pathway) in the perception of tinnitus because of silence (auditory deprivation). The procedure will use the contralateral suppression of transient evoked otoacoustic emissions for the assessment. This study was designed to provide insight into: the physiology of connecting neural pathway between (a) the "afferent auditory pathway and the medial olivocochlear efferent" pathway, (b) the "medial olivocochlear efferent and outer hair cells," and (c) the "outer hair cells and the afferent pathway." Positive results may be applied to understand the underlying pathophysiology of tinnitus and may help to select different treatment options in those tinnitus patients with sensory deprivation caused by hearing loss or in patients with chronic tinnitus without hearing loss.

CHAPTER II

REVIEW OF THE LITERATURE

This review of the literature will describe what is known concerning the relationship between tinnitus perception and the possible role of the efferent auditory pathway in tinnitus perception. The contralateral suppression of otoacoustic emissions (OAEs) provides a valuable technique for identifying the function of the efferent auditory pathway. An altered or abnormal efferent auditory pathway function has been observed in tinnitus patients using transient evoked otoacoustic emissions (Geven, Wit, De kleine, & Van Dijk, 2012; Lalaki et al., 2011) as an objective measure. Thus, the literature review will make the case as to why otoacoustic emissions may be used to shed light on the neurophysiology underlying tinnitus. Studies pertaining to tinnitus, the efferent pathway and otoacoustic emissions will be reviewed. Therefore, this literature review will focus on the following topics: (a) tinnitus (definition, prevalence, physiological aspects, relation to sensory deprivation and short-term sensory deprivation); (b) efferent auditory pathway (its anatomy and role in suppression of otoacoustic emissions); and (c) otoacoustic emissions (their types, the relation of suppression of otoacoustic emissions to tinnitus and the suppression of transient otoacoustic emissions).

Tinnitus

Definition of Tinnitus

Tinnitus is the perception of sound in the absence of an external auditory stimulus (Møller, 2007). Tinnitus can be classified into two types:

1. Objective tinnitus: the perception of sound due to the physical source inside the body. These sounds are usually produced by internal function in the body's circulatory (blood flow) and somatic (musculo-skeleton movement) system. Almost all the causes of this type of tinnitus can be diagnosed by magnetic resonance imaging or magnetic resonance angiography (Sismanis, 1998, 2003).
2. Subjective tinnitus: the perception of sound when there is no inside or outside sound source present. This may be due to auditory and neurological reaction to hearing loss.

This study will focus on subjective tinnitus, as very little information is known about the pathophysiology of this type of tinnitus.

Prevalence of Tinnitus

According to American Tinnitus Association and the National Institute of Health (NIH), an estimated 50 million people in the U.S. experience chronic tinnitus or ringing in the ears. Of those, 16 million have sought medical attention for their tinnitus; and two to three million are completely disabled from it (data collected and analyzed from the 1999-2004 National Health Interview Survey conducted by the Centers for Disease Control). The prevalence of tinnitus in children and geriatric population is 20-40% and

15%, respectively. The prevalence in young adults who perceive continuous tinnitus for >5 min is approximately 25%.

Tinnitus and Gender

Typically, epidemiological studies of prevalence show that tinnitus may occur more often in men, but results are inconsistent (Møller, 2011). No significant differences in tinnitus perception were observed between male and females when silence/sensory deprivation was employed to trigger tinnitus (Knobel & Sanchez, 2008; Tucker et al., 2005).

Tinnitus and Race

According to the National Health and Nutrition Examination Surveys among U.S. adults (1999-2004), the prevalence of frequent experiences of tinnitus is highest among the non-Hispanic whites with decreases in prevalence among Hispanic, Black, and other races (Shargorodsky, Curhan, & Farwell, 2010). Tucker et al. (2005) found a significant difference in tinnitus perception between Caucasian and African American subjects when silence was employed as the tinnitus-triggering factor. Caucasians perceived tinnitus more often than African Americans after 20 minutes of silence.

Tinnitus and Location of Perception

Research on tinnitus showed that tinnitus could be perceived unilaterally (left ear only or right ear only) or bilaterally (both ears) or perceived as located inside the head. Hallberg and Erlandsson (1993) investigated predominance of left ear tinnitus perception in patients with complaints about tinnitus and in the patients without complaints about tinnitus. Tinnitus was reported to be perceived in the left ear in 42% versus 26% in the

right ear of tinnitus patients. The percentages were 30% (left-eared tinnitus) and 25% (right-eared) for the patients without complaints about their tinnitus. Tinnitus was reported “in the head” by 14% of complainers and 6% of the non-complainers. Hiller and Goebel (2006) also reported a predominance of left-sided tinnitus (29.1%) versus right-sided (20%). This study included 4995 members of German Tinnitus League. Indeed, the binaural perception of tinnitus was more prevalent (44.9%) in these subjects than either sided tinnitus.” This study also reported 23.7% of subjects perceived tinnitus centrally (in the head). Similarly, Stouffer and Tyler (1990) reported a higher incidence of tinnitus in left ear (21.4%) than in right (15.9%). The binaural perception was reported at 20.3%. Thus, research supports a predominance of left-sided tinnitus over right-side tinnitus. The incidence of bilateral tinnitus was between 20% and 48%.

Physiological Aspects of Tinnitus (Possible Generators)

Tinnitus can be linked to peripheral ear pathology (e.g., Meniere’s disease, otitis media, Eustachian tube dysfunction, or it can be linked to dysfunction of the central auditory nervous system (CANS). Neuroscience research in tinnitus has provided strong evidence that “significant tinnitus” or continuous tinnitus is a “central auditory processing disorder” (Eggermont, 2012). Such studies have demonstrated the involvement of one or more aspects of the nervous system other than the auditory system (e.g., limbic system, autonomic nervous system, etc.), which interact with the auditory nervous system to trigger tinnitus (Jastreboff, 1999). Lower levels of salivary alpha amylase (stress-related biomarker in salivary secretion) were found in male subjects with tinnitus than subjects without tinnitus, suggesting impaired sympathetic activity in the

subjects with tinnitus (Alsalman, Tucker & Vanneste, 2016). See Appendix A for the abbreviations for the major anatomical structures within the auditory system.

Models of Tinnitus

Subjective tinnitus occurs more commonly than objective tinnitus. In recent years, tinnitus has been investigated as a central auditory processing disorder, although it has underlying peripheral triggers (Eggermont, 2012). Research has shown that the human central auditory system interacts with human limbic and autonomic nervous system that results in a complex neural mechanism involved in the perception of tinnitus (Jastreboff, 1999). Because of these interactions, different underlying pathologies may act as a triggering factor in tinnitus. Therefore, researchers have produced several different models of tinnitus derived from animal studies to characterize the pathophysiology of tinnitus and to identify the neural structures in humans likely involved in the perception of chronic tinnitus. Several of these models are discussed below.

The Salicylate Model. Eggermont (2012) reviewed the Salicylate, Sensorineural, Somatic, and Neural Synchrony models of tinnitus. Salicylate (aspirin: non-steroidal anti-inflammatory drug) is an ototoxic drug and can act negatively on both the peripheral and central auditory nervous system by affecting the electromotility of Outer Hair Cells. Salicylate can be a tinnitus-inducing agent (Cazals, 2000). Greeson and Raphael (2009) found that salicylate affects the electromotility of outer hair cell by its direct interaction with the prestin protein in the wall of the outer hair cell causing temporary hearing loss.

Wu, Lv, Kim, Yamoah, and Nuttall (2010) found that a higher dose of salicylate is required in humans than animals to induce hearing loss. This study suggested that

salicylates could also reduce the driving force (Potassium Ion flow through the outer hair cell) required for transduction current and electromotility in outer hair cell by blocking KCNQ4 ion channel.

Salicylate can also disrupt inner hair cell (IHC) function. Research has shown that salicylates can disrupt the arachidonic acid cycle. In the normal physiological process, enzyme cyclooxygenase (COX) metabolizes arachidonic acid into prostaglandins and tromboxanes. Salicylate inhibits the prostaglandin synthesis through inhibition of cyclooxygenase causing interference in arachidonic acid cycle in the IHCs. Such interference can cause an up-regulation of N-methyl-D-aspartate (NMDA) receptor activity in the synaptic junctions between IHC and auditory nerve fibers. This disruption increases the probability of NMDA receptor channel opening and potentially leads to increased spontaneous firing rates in a subset of auditory nerve fibers (Guitton et al., 2003). The application of NMDA antagonist in the perilymphatic fluid of the cochlea strongly reduces the behavioral indicator of tinnitus in rats, suggesting the possible role of NMDA receptor in the generation of salicylate–induced tinnitus through a mechanism involving the cyclooxygenase pathway. The direct explanation on the molecular mechanism of such pathway involving cyclooxygenase and NMDA receptors needs to be determined.

The harmful effects of salicylate on the central auditory system (CAS) in animals include reduced activity in gamma-Aminobutyric acid (GABA) activity, which increases the gain (amplitude) of sound processing in the central auditory system. GABA is the inhibitory neurotransmitter of the central nervous system. Reduced activity of GABA in

inferior colliculus consequently increases neural firing in IC and may result in the increased sound perception (Bauer, Brozoski, Holder, & Caspary, 2000). Thus, tinnitus perception can be attributed to the altered activity in the outer hair cell motor protein or arachnoid acid cycle in the inner hair cell or GABAergic activity within the inferior colliculus or combination of two or more of these changes.

The Sensorineural Model. Ototoxicity affects the sensory end organs (OHC) and neural structures (auditory nerve fibers). Prolonged noise exposure can also cause OHC damage (by the formation of reactive oxygen species, ROS and reactive nitrogen species, RNS; together called ROS/RNS) and permanent loss of ganglion cells that innervate inner hair cells (Henderson, Bielefeld, Harris, & Hu, 2006). These changes generally cause a reduction in spontaneous firing rates of auditory nerve fibers and remove the peripheral inhibitory effect. Therefore, these changes cause hyperactivity in the dorsal cochlear nucleus (DCN). This results in tonotopic map reorganization in cortical areas (Eggermont & Komiya, 2000). Such imbalance between inhibition and excitation leads to an increased spontaneous firing rate (SFR) and perception of tinnitus. These neural and sensory changes could contribute to tinnitus perception.

The Somatic Tinnitus Model. The auditory input from auditory nerve goes to the fusiform cell (FC), and the giant cell in the dorsal cochlear nucleus (DCN); then, it is redirected to the inferior colliculus (Auditory system). Fusiform cells and giant cells also receive the input from the trigeminal and dorsal column systems (somatosensory system). Inputs from trigeminal and dorsal column activate the granule cells, which send an activation signal to fusiform and giant cells through the parallel fibers. These stimulations

also turn on the cartwheel cells. Cartwheel cells inhibit the fusiform cells and may also stimulate or inhibit other cartwheel cells (somatosensory system). Thus, an interaction between auditory and somatosensory inputs from the nervous system at the level of fusiform cell layer provides for generation and/or modulation of tinnitus (tinnitus related to the head, neck or jaw injuries) (Oertel & Young, 2004).

In the case of peripheral hearing loss, the spontaneous firing rate of the neurons in the dorsal cochlear nucleus increases because of the sensory deprivation (Finlayson & Kaltenbach, 2009). Thus, the neural synapse strength for auditory input decreases and the somatosensory input synapse strength increases. This may occur as a compensation for the lost auditory input because of peripheral hearing loss in which neural plasticity might play a role (Møller, 2011). Such neural plastic changes lead to enhanced suppression due to inputs from trigeminal and dorsal column systems. Thus, increased spontaneous firing rate in dorsal cochlear nucleus due to deprivation and strengthening of a somatosensory synapse may underlie the perception of change in tinnitus loudness associated with the masticatory abnormality (as the mandibular branch of trigeminal nerve innervates the temporomadibular joint).

The Neural Synchrony Model. Rajan and Irvine (1998) described the phenomenon of neural synchrony through the over-representation of tonotopicity in the auditory cortex of a cat. The cat sustained high-frequency hearing loss due to noise trauma. This high-frequency cochlear damage disconnects the peripheral auditory input to the tonotopic map in the thalamocortical region. Because of this lack of auditory input, auditory neurons in the affected region of the thalamocortical region begins to respond

preferentially to input conveyed by horizontal fibers. Consequently, affected neurons begin to express the tuning preference of their neighbors. Over the period, such synchronous firing of affected neuron leads to an overrepresentation of edge frequencies in the tonotopic gradient in cortical region and cortical tonotopic map reorganizes.

It has been proposed that this overrepresentation of edge frequencies may correspond to the tinnitus percept and the tinnitus pitch could be matched to the edge frequency of the normal hearing.

Neurophysiological (Limbic System/Autonomic Nervous System) Model of Tinnitus Disturbance. Jastreboff (1999) hypothesized that there are an increased agitation and awareness of tinnitus and this occurs due to the interaction of limbic and autonomic nervous system (ANS) (see Figure 1). The ability to learn conditioned reflexes and the role of "emotion" in the control of behavior, memory, motivation, and mood involve the limbic system and autonomic nervous system. Thus, the agitation of the person (involving autonomic nervous system changes) affects limbic activation (involved in emotional expression), which in turn affects the central auditory nervous system resulting in the experience of tinnitus.

The temporal coincidence of sensory stimuli with negative (or positive) reinforcement is sufficient to generate a conditioned reflex (Jastreboff, 1999). Any stimulus that triggers agitation (tinnitus itself may be a conditioned stimulus for triggering agitation) can become a conditioned stimulus for tinnitus. However, the stimulus that is registered in our memory does not reach the level of awareness.

Consequently, no reaction is generated, leading to the habituation of the perception of the stimuli (Jastreboff, 1999). It means,

> As long as the sensory stimulus is limited in time and there is no functional dependence of the stimulus, this conditioned reaction will gradually disappear (habituate) due to passive extinction of the reflex (the sensory stimulus is present but is not accompanied by a reinforcement). (Jastreboff, 1999, p. 34)

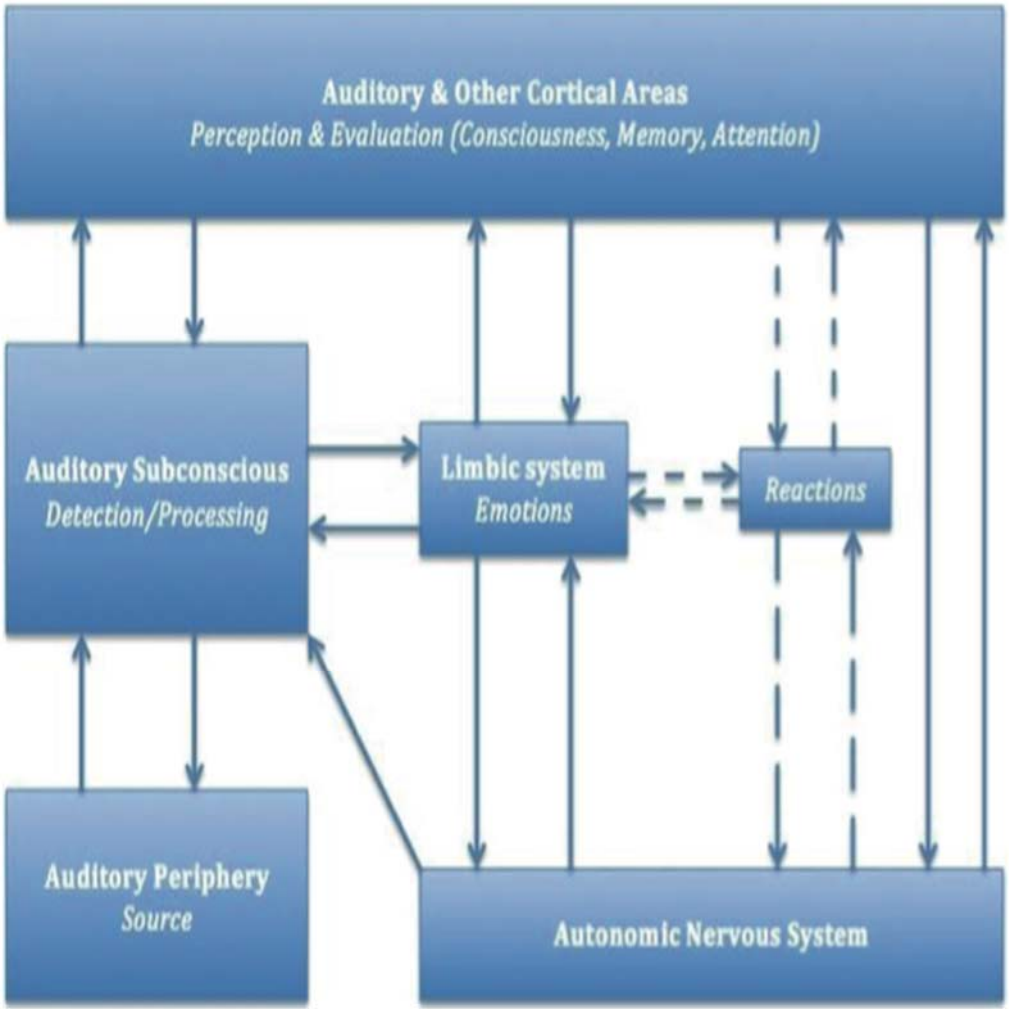

Figure 1. The Neurophysiological Model of Tinnitus Disturbance. Re-Created from Jastreboff, P. J. (1999). *The Neurophysiological Model of Tinnitus and Hyperacusis.* Proceedings of The Sixth International Tinnitus Seminar, 1999. Cambridge, UK).

The unknown source for the auditory stimuli like tinnitus when first experienced creates consternation in the person because he/she is unsure how this perceived sound is being heard when there is no identifiable stimulus in the surrounding environment. This experience creates the negative feeling of discomfort, distress, and negative emotional response and the autonomic nervous system gets activated. Thus, the repeated temporal coincidence of this unknown sensory stimulus (tinnitus) with the negative reinforcement (negative feeling of discomfort, distress, etc.) creates a conditioned reflex and forms a vicious cycle of physiological and non-physiological factors in a patient with chronic tinnitus. In addition, any significant changes in life (death of family members/friend, loss of job, etc.) may exacerbate the negative emotions, feelings, and distress, leading to an exacerbation in the tinnitus perception in terms of intensity because of conditioned reflexes.

In conclusion, the contribution of auditory structures (generators) such as OHC, auditory nerve, cochlear nucleus, inferior colliculus, primary auditory area, limbic and autonomic nervous system in various combinations may be responsible for the perception of tinnitus.

All the models address tinnitus perception in pathological ears associated with some degree of hearing loss but pathophysiology underlying tinnitus perception in people with normal hearing remains elusive and unclear. Barnea, Attias, Gold, and Shahar (1990) found 8-10% of persons with tinnitus have normal hearing. Another study by Jastreboff and Jastreboff (2003) mentioned 20% of patients with tinnitus had normal hearing. Therefore, hearing loss is neither required nor sufficient condition for the

tinnitus initiation. In the next section, the connection between chronic tinnitus and hearing loss will be discussed.

Tinnitus and Hearing Loss (Sensory Deprivation)

The effect of sensory deprivation (as documented in the nervous systems in animals) is profound. Sensory deprivation can also occur in many life stages. Early in fetal development, sensory stimulation guides the anatomical and functional development of nervous system. Therefore, sound deprivation likely has a profound effect on the early development of the auditory nervous system and this may extend to young individuals more than to adults. Two types of neural changes can occur because of sensory deprivation to the auditory system. One, the increase in the gain of the auditory nervous system due to changes excitation and inhibition balance and two, activation of neural plasticity including a change in synaptic efficacy and sprouting of axons (Møller, 2006).

Since any disorder that can cause hearing loss produces auditory deprivation, the degree to which an individual experiences auditory sensory deprivation depends on the degree of hearing loss. Ear canal blockage, middle ear disorders, and disorders of the cochlea can cause hearing loss ranging from mild to severe and from temporary to permanent.

Tinnitus is common in individuals with a noise-induced hearing loss (an imposed form of sensory deprivation on the auditory system). Eggermont and Roberts (2004) postulated that increased spontaneous firing rate (SFR) (in the brainstem and auditory cortex), increased neural synchrony (auditory thalamic structures and primary auditory cortex) and tonotopic cortical map reorganization are potential neural substrates of

tinnitus. To understand the neural substrates of tinnitus, structural changes in the auditory nervous system resulting from partial hearing loss because of noise exposure, unilateral or bilateral cochlear ablation, and removal of middle ear ossicles (three bones in the middle ear) need to be assessed. Because noise exposure is likely the most common source of auditory deprivation, the effects of noise exposure on the structures of the auditory system and on tinnitus perception will be reviewed next.

Structural and Physiological Changes in the Peripheral and Central Auditory Nervous System (CANS) Due to Noise Exposure

Noise exposure can induce temporary or permanent hearing loss depending on the level and duration of noise exposure. Often, tinnitus emerges as an associated symptom with noise-induced hearing loss (Dancer, Henderson, Salvi, & Hamernik, 1992). Due to our limited understanding of the biological basis of tinnitus, tinnitus in noise-induced hearing loss cases become interesting symptom because noise exposure primarily damages the periphery (cochlea) while evidence indicates that tinnitus is often clearly of central origin. Therefore, it is important to understand the peripheral and central auditory changes due to noise exposure.

Changes in Cochlear Hair Cells and Auditory Nerve

One example of structural and physiologic changes in the inner ear due to noise exposure is reactive oxygen species (ROS). Overexposure to noise can permanently damage the outer hair cells inside the cochlea and may cause permanent hearing loss involving type I spiral ganglion cells that innervate the inner hair cell (Kiang, Liberman, & Levine, 1976). Henderson and colleagues (2006) observed the mechanism that noise

exposure can produce the reactive oxygen species (ROS) within the cochlea. Reactive oxygen species are chemically reactive species containing oxygen. Examples of reactive oxygen species are peroxides, superoxide, and hydroxyl radical.

Noise can affect the function of mitochondria inside the cochlea. During noise exposure, the mitochondria in the outer hair cell (OHC) expend large amounts of energy through “aerobic respiration” as outer hair cells need energy for their motility in response to sound. High oxygen use creates large amounts of superoxide as an unwanted product, which creates higher levels of other reactive oxygen species in the cochlea as the superoxide reacts with other molecules (Halliwell & Gutteridge, 1985).

In addition to the overdriving of the mitochondria, another cause of increased reactive oxygen species in the cochlea is the excitotoxicity and ischemia/reperfusion. Such excitotoxicity can generate event of downstream apoptotic cell death pathways because of DNA, protein damage, and lipid peroxidation. Since glutamate acts as an excitatory neurotransmitter at the synapses between the inner hair cell (IHC) and auditory nerve fibers (ANF), then when the inner hair cell becomes highly active during high-level noise exposure this can produce excitotoxicity of auditory nerve fibers. The inner hair cell high activity leads to the release of a large amount of glutamate into the synapses with type-I fibers of the VIIIth nerve. This excess amount of glutamate causes overstimulation of postsynaptic cells via their glutamate receptors, leading to swelling of postsynaptic cell bodies and dendrites (Kandel, Schwartz, & Jessell, 2000). This is a potential source for excitotoxicity and the apoptosis of neural cells.

Changes in the Dorsal Cochlear Nucleus (DCN)

The auditory nerves almost innervate all the neurons (approximately 100,000) in the cochlear nucleus (Moore, 1987). One source for tinnitus generation may be the dorsal cochlear nucleus, the first neural station inside the brainstem along the central auditory nervous system pathway. Several researchers have theorized that changes in the anatomy and physiology of the dorsal cochlear nucleus may be a neurogenerator of chronic tinnitus.

Kaltenbach, Zhang, and Afman (2000) observed an increase in spontaneous firing rate in superficial neurons in the dorsal cochlear nucleus of hamster 5 days after the noise exposure of 10-kHz tone at levels between 125-130 sound pressure level (SPL) for a period of 4 hours. Similar results were observed when the exposure was 10 kHz tone for 2 h at 80 dB sound pressure level (Kaltenbach, Zhang, & Finlayson, 2005). In both studies, hair cells and their stereocilia were intact. These findings suggest that extended overstimulation of cochlear hair cells can result in the generation of hyperactivity in the dorsal cochlear nucleus without apparent loss of hair cell or stereocilia. Thus, spontaneous firing rate appears to be independent of cochlear input in the dorsal cochlear nucleus. It has also been observed that hyperactivity in the dorsal cochlear nucleus in response to an 80 dB sound pressure level stimulus had immediate onset than for 125-130 dB sound pressure level stimulus. The strength of the behavioral testing of tinnitus in noise-exposed hamster was related to the increase in spontaneous firing rate in the dorsal cochlear nucleus. In addition, sectioning of the dorsal cochlear nucleus to make it isolated from its adjacent brainstem structures did not significantly affect the spontaneous firing

rate in the dorsal cochlear nucleus (Kaltenbach, Zacharek, Zhang, & Frederick, 2004). This shows that changes in the spontaneous firing rates in the dorsal cochlear nucleus depend on the inputs and neural network to and from the adjacent structures.

Two studies, one by Zhou and Shore (2006) and the other by Ma and Young (2006), produced contradictory results concerning the lack of increased spontaneous firing rate inside the dorsal cochlear nucleus after the noise exposure. The study by Ma and Young (2006) was performed on cats instead of hamsters. Thus, there may be species a difference in the changes in the auditory system after noise exposure. Zhang, Kaltenbach, Godfrey, and Wang (2006) observed enhanced hyperactivity in the dorsal cochlear nucleus after the sectioning of dorsal acoustic stria (a structure that provides inputs to the dorsal cochlear nucleus) suggesting it may have an inhibitory effect on the dorsal cochlear nucleus. The behavioral tests (continuous pressing of the lever during the period of silence because of perception tinnitus) for tinnitus in Long-Evans rats after the unilateral exposure to a 60-min duration octave band noise centered at 16 kHz at 110 SPL showed the presence of tinnitus at approximately 20 kHz before and after bilateral ablation of the dorsal cochlear nucleus performed between 3 and 5 months after the acoustic trauma. This finding suggests increased spontaneous firing rate in the dorsal cochlear nucleus is not entirely the initiator of behavioral signs of tinnitus.

Changes in the Ventral Cochlear Nucleus (VCN)

Another source for the generation of tinnitus may be the ventral cochlear nucleus (VCN). Vogler, Robertson, and Mulders (2011) report a study in which a guinea pig was exposed to 10 kHz tones presented at 124 dB SPL for 2 hours. The spontaneous firing

rate in noise-exposed ears was significantly elevated in the ventral cochlear nucleus after a two-week recovery period. In contrast, cats exposed to pink noise-exposed to pink noise for half an hour at 105 dB SPL, producing an average threshold shift of 30 dB in the 2-6 kHz region did not show a significant difference in SFR in the anterior ventral cochlear nucleus (AVCN) post-exposure (Van Heusden & Smoorenburg, 1983). It is unclear if changes to the ventral cochlear nucleus are a source of tinnitus generation in humans.

Changes in the Inferior Colliculus (IC)

Another potential source of tinnitus generation in humans might be the changes in the inferior colliculus (IC) resulting from exposure to noise. These changes can result in either an increase in spontaneous firing rate of inferior colliculus fibers or a hyperactivity of inferior colliculus fibers. Mulders and Robertson (2009) exposed guinea pigs to 10 kHz tone at 124 dB SPL for 1 hour and observed that acoustic trauma did not immediately initiate changes in spontaneous firing rate in the inferior colliculus. However, increase in the spontaneous firing rate was reported during the recovery period. This increased spontaneous firing rate in inferior colliculus disappeared after cochlear ablation. Thus, changes in spontaneous firing rate in inferior colliculus seem to depend on the input from the cochlea.

Mulders, Seluakumaran, and Robertson (2010) confirmed the previous findings that the hyperactivity in the inferior colliculus increases during the recovery period after the acoustic trauma. In this study, they also electrically stimulated the olivocochlear system (known to decrease the auditory nerve fiber activity) and found that olivocochlear system reduced the hyperactivity in the inferior colliculus by reducing the cochlear input

through a suppressive effect on auditory nerve fibers. Dong, Mulders, Rodger, Woo, and Robertson (2010) also observed supporting findings that the spontaneous firing rate in the inferior colliculus did not increase immediately after noise exposure but did after 2 weeks. The significant increase in the spontaneous firing rate in the central nucleus of the inferior colliculus (ICc) of the noise-exposed (4kHz tone at 85-dB for 1h) chinchillas was observed at 2 weeks post-exposure. These animals showed behavioral evidence of tinnitus at the same time of the recording activity in the inferior colliculus. Thus, it appears that noise exposure can cause changes in the inferior colliculus that might contribute to tinnitus generation.

Changes in the Auditory Cortex

The location for changes in the central auditory nervous system that most likely contributes to tinnitus generation by researchers appears to be the auditory cortex. These changes include a remapping of frequency regions inside the primary auditory cortex and changes in spontaneous neural activity. Eggermont and Komiya (2000) observed profound reorganization of the frequency map in the primary auditory cortex of juvenile cats (5-6 weeks old) after the exposure to loud 6 kHz tone. The noise exposure caused mild to moderate high-frequency hearing loss. The region in primary auditory cortex between 6 and 10 kHz was greatly expanded in the noise trauma induced felines and covered the cortical areas that would normally include frequencies between 10 and 40 kHz.

Spontaneous activity in the reorganized part of the cortex was also significantly increased in cats that had been exposed to noise. This spontaneous neural activity could

be the result of increased spontaneous firing rate in subcortical structures such as the high-frequency part of the inferior colliculus or dorsal cochlear nucleus as noted in noise trauma induced studies in animals in the previous section. The observed increase in spontaneous firing rate in the reorganized region of primary auditory cortex found in the present study could be a substrate for tinnitus.

Noreña and Eggermont (2005) conducted a study in cats to observe the effect of enriched acoustic environment after the noise trauma-induced hearing loss. The results of this study showed noise-induced hearing loss was limited by the targeted acoustic stimulation. This targeted acoustic stimulation was given immediately after the trauma. This study also found that the targeted acoustic stimulation in hearing loss frequency region after noise-induced hearing loss prevented the cortical tonotopic map reorganization in cats. The other group of cats who were kept in silence after noise exposure showed such reorganization in the primary auditory cortex. Noise exposure causes peripheral hearing loss (decrease in auditory nerve firing rates) and changes the excitatory and inhibitory balance between the periphery and central structures of the auditory system as noted earlier (Eggermont & Komiya, 2000). In this study, stimulation in hearing loss frequency range at supra-threshold level compensated for the decrease in auditory nerve fiber firing rates and thereby prevented the cascade of central changes (release from inhibition) that would normally lead to cortical tonotopic map reorganization (Noreña & Eggermont, 2003).

In the subsequent follow-up study, Noreña, Gourevich, Aizawa, and Eggermont (2006) investigated the effect of enhanced acoustic environment on neural firing rates and

neural synchrony (i.e., a sign of tinnitus) after the noise-induced hearing loss in cats. When the enhanced acoustic environment with a spectrum corresponding to the frequency band of the hearing loss was provided after the trauma, tonotopical map, spontaneous firing rate, and synchrony were unchanged. Thus, post-trauma acoustic stimulation might prevent the occurrence of tinnitus if trauma induced tinnitus is related to an increase in spontaneous firing rate or synchrony in the primary auditory cortex. In this study, authors also found that acoustic stimulation in low-frequency range (normal hearing frequencies) had little or no effect.

Changes Due to Ossicular Removal (Conductive Hearing Loss) and Cochlear Ablation (Deafness)

Researchers have reported that changes to the peripheral auditory structures, such as removing the ossicles (middle ear bones) or ablation of the cochlea itself also resulted in changes in physiology in higher centers within the central auditory nervous system where tinnitus may be generated. Potashner, Suneja, and Benson (1997) observed the cochlear nerve degeneration and degeneration in the central auditory nuclei after the unilateral ossicles removal. Degeneration of fine fibers and granulated axons in the cochlear nucleus were also observed (more abundant on the ipsilateral side) but only after 112 days of ossicle removal. This suggests that without cochlear damage, hearing loss created by the ossicular removal still had the degenerating effect in cochlear nucleus but only after several months. Sumner, Tucci, and Shore (2005) found the significant increase in the spontaneous firing rate of ventral cochlear nucleus neurons immediately after ossicular removal over first 8 hours that declined with time but did not reach normal

value by 14 days. This finding suggests that the peripheral afferent auditory inhibitory input is necessary to keep a check on the spontaneous firing rate of the ventral cochlear neurons. In addition, later decline in spontaneous firing rate suggests the rapid compensatory excitatory contralateral input to the ventral cochlear nucleus.

Ablation of the left cochlea resulted in the degeneration of large, intermediate, and fine fibers in the ipsilateral anterior ventral cochlear nucleus (AVCN) and posterior ventral cochlear nucleus (PVCN) after 7 days. Ipsilateral dorsal cochlear nucleus had dense degeneration near the dorsal acoustic stria (Potashner et al., 1997). This suggests that ablation starts degeneration process in the cochlear nucleus within a week. Koerber, Pfeiffer, Warr, and Kiang (1966) observed the cessation of almost all the activity in the ventral cochlear nucleus immediately after the complete cochlear destruction while the activity in the dorsal cochlear nucleus was relatively unaffected. Similarly, Zacharek, Kaltenbach, Mathog, and Zhang (2002) also observed no significant effect in spontaneous firing rate in the dorsal cochlear nucleus after 30 days of partial and complete cochlear ablation. Partial cochlear ablation initiated an increase in spontaneous firing rate in the ventral cochlear nucleus (Bledsoe et al., 2009).

Thus, it may be inferred that sensory deprivation due to unilateral or bilateral cochlear ablation has a different effect on auditory structures than the sensory deprivation effect of ossicle removal. In addition, sensory deprivation due to cochlear ablation has different effects on auditory structures than the effect of sensory deprivation due to hearing loss because of noise trauma (exposure).

Causes for Tinnitus Emergence

Excitatory-Inhibitory Imbalance and Neural Reorganization

Studies in the previous sections suggested the possible role of many different parts of the nervous system in tinnitus. The possible reasons for the tinnitus perception are:

1. An altered spontaneous activity that can be different at different levels of the auditory system, and/or
2. Less neural excitation in the periphery of the ascending auditory pathway but greater activity in central auditory structures, and/or
3. Increased neural synchrony of the neural firing, and/or
4. Increased neural synchrony of the firing in large groups of the nerve cells.

To understand the possible pathophysiology, which might be associated with neural changes resulting from the sensory deprivation caused by a different disturbance (noise trauma, ossicular removal or cochlear ablation), the phenomenon of excitatory-inhibitory imbalance and neural reorganization (neuroplasticity) need to be understood.

Excitatory-Inhibitory Imbalance of Neurotransmitters

Changes in the neurotransmitters and neuromodulators cause the changes in the activity of the auditory structures. Muly, Gross, and Potashner (2004) studied the effect of noise trauma in chinchilla cochlear nucleus. The noise trauma was unilateral and the other ear was protected by silicon plug. In the noise-exposed ear, glutamatergic synaptic release in the ipsilateral cochlear nucleus was elevated and uptake was depressed during the first-week post-exposure and before the cochlear nerve axons degenerate. This, in

turn, created hyperactivity of glutamatergic transmission in the cochlear nucleus in which the excitotoxic mechanism might be involved. By the end of second-week post exposure, the cochlear nerve fibers degenerated and the glutamatergic synaptic release and uptake in the cochlear nucleus became abolished. By 90 days post exposure, the plastic changes occurred in the cochlear nucleus due to the reappearance of transmitter release and elevation of AMPA receptor (ionotropic transmembrane receptor for glutamate that mediates fast synaptic transmission in the central nervous system) binding. Such changes were absent in the ear with the plug (non-exposed ear). The altered AMPA receptor binding activity and glutamatergic release suggested up regulatory activity in the cochlear nucleus that may contribute to tinnitus.

The study by Potashner et al. (1997) discussed earlier showed the changes in the glutamatergic presynaptic release and glutamate inactivation in the cochlear nucleus, superior olivary complex (SOC) and midbrain of the adult guinea pigs after the unilateral ossicle removal and cochlear ablation. After ossicular removal, delay in degeneration of CN fibers was consistent with the delay (after 145 days of ossicle removal) in the decreased release and uptake of glutamate, which suggest the regulatory weakening of excitatory glutamatergic transmission. On the other hand, the cochlear ablation, which deafferented the cochlear nucleus, resulted in the deficiency in release and uptake of glutamate within just 2 days after ablation. Such deficiency also resulted in abundant fiber degeneration in the cochlear nucleus by 7 days. Subsequently, the residual release and uptake increased and in turn strengthened excitatory glutamatergic transmission. Similar changes were found in the contralateral (opposite) cochlear nucleus irrespective

of the type of lesion suggesting that changes in the lesioned ear may also initiate the regulatory synaptic changes in the contralateral CN. Both lesions induced abnormally strengthened glutamatergic transmission in the superior olivary complex and the midbrain. Potashner et al. (1997) suggested that the strengthening of excitatory glutamatergic transmission might facilitate and maintain symptoms such as loudness recruitment and tinnitus that often accompany hearing loss.

Suneja, Potashner, and Benson (2000) observed bilateral central nucleus of inferior colliculus (ICc) decrease in AMPA binding 30 days after unilateral cochlear ablation followed by an increase at 60 days. An increase of AMPA receptor subunit (GluR2, GluR3, and GluR kainite) expression was detected in the central nucleus of inferior colliculus from 3 to 90 days following bilateral cochlear ablation (Holt et al., 2005). These studies showed that the AMPA receptor changes occurring in the central nucleus of inferior colliculus take a longer time than in the cochlear nucleus.

Unilateral ossicle removal induced a decline in glycine release and elevated glycine uptake in the anterior ventral cochlear nucleus and dorsal cochlear nucleus in adult guinea pigs. Similar findings were observed in the dorsal cochlear nucleus after the unilateral cochlear ablation (Suneja, Benson, & Potashner, 1998; Suneja, Potashner, & Benson, 1998). Such changes were consistent with the down-regulation of the presynaptic component of glycinergic inhibitory transmission along with the swift removal of extracellular glycine. Such effects suggest a weakening of glycinergic inhibitory transmission. Argence et al. (2006) found decreased expression of the α1

subunit of GlyR in the contralateral central nucleus of inferior colliculus after unilateral cochlear ablation.

These findings suggest the long-term deficits in glycinergic synaptic inhibition in most of the cochlear nucleus, anterior ventral cochlear nucleus, and the dorsal cochlear nucleus of the opposite side because of cochlear ablation. The mechanisms involved are (a) down-regulation of postsynaptic GlyR activity in the ventral cochlear nucleus and (b) down-regulation of the synaptic release of glycine in the dorsal cochlear nucleus and faster removal of extracellular glycine. These mechanisms may initiate the long-term hyperexcitability and increased spontaneous firing rate in the dorsal cochlear nucleus and may contribute to the tinnitus perception.

Szczepaniak and Møller (1995) observed a decrease in GABA-mediated inhibition in the inferior colliculus. In the studies by Suneja, Benson, et al. (1998) and Suneja, Potashner, et al. (1998), the early changes in the contralateral central nucleus of inferior colliculus were consistent with an early weakening of GABAergic inhibition. The late strengthening of GABAergic inhibition may have developed in response to the up-regulation of transmitter release from the glutamatergic synaptic endings in the central nucleus of the inferior colliculus.

Thus, the type of procedure for creating peripheral lesions (noise exposure, cochlear ablation, and ossicular removal) affects the molecular outcomes by creating sensory deprivation. Such changes in excitatory and inhibitory synapses can be interpreted as follows:

1. Auditory nerve fibers have both excitatory and inhibitory response areas (Sachs & Kiang, 1968) and inhibition is a form of suppression that cochlear outputs impose on the higher centers (Ruggero, 1992). This means that sounds such as a tone will cause both inhibition and excitation in the auditory nervous system through synapses. The basilar membrane has the receptive fields for the certain frequencies (tonotopicity) and such tonotopic arrangement can be seen throughout the auditory nervous system. It enables the auditory system to have the lateral inhibition or suppression similar to what is in the visual system. Lateral inhibition is the capacity of the neurons of excited neurons to reduce the activity of neighboring neurons. Thus, if the peripheral pathology reduces the input in certain frequencies, it can reduce the lateral inhibition in higher auditory centers (dorsal cochlear nucleus, inferior colliculus) and this may enable the neighboring neurons to become sufficiently active to produce awareness of sound without an external source of the sound, leading to the perception of tinnitus (Rajan & Irvine, 1998).
2. Evidence supports the findings that high-frequency sounds elicit the stronger inhibitory response in the neurons in the cochlear nucleus than low frequencies. Acoustic trauma commonly causes the high-frequency hearing loss and may cause tinnitus because of reduced high-frequency lateral inhibition. The inferior colliculus has significant interaction between excitation and inhibition.

Neural Reorganization in Auditory Cortex

Many forms of tinnitus have been linked to neural plasticity (Bartels, Staal, & Albers, 2007) and thus tinnitus is considered a "plastic disorder" (Møller, 2008). Sensory deprivation is the strongest premotor of neural plasticity (Møller, 2006). The nervous system can change its function because of neural plasticity in synaptic connections. The person who is placed in the sound proof booth for some time experiences the tinnitus that may be a result of the immediate effect of neural changes.

Neural plasticity can cause normally ineffective synapses, typically masked by normally dominant synapses, to become active (Møller, 2001, 2006). Such neural plasticity can play a role when the non-classical auditory pathway (extra-lemniscal pathway) receives the auditory input from the ear and activates its neural connection to sensory receptor of other sensory systems (e.g., somatosensory). Non-classical auditory pathway also has neural connections with amygdala and other limbic structures (LeDoux, 1992). It also receives neural inputs from dorsal and medial thalamus (Møller, 2003). The non-classical pathway has been observed to play a role in tinnitus perception (Møller, Møller, & Yokota, 1992). Non-classical or extralemniscal pathway consists of the external nucleus of inferior colliculus, the magnocellular nucleus of the medial geniculate body, dorsal cochlear nucleus and secondary auditory cortex (Eggermont, 2005). Changes in the spontaneous activity of the extralemniscal pathway have been linked to the tinnitus generation. Chen and Jastreboff (1995) observed the increased spontaneous activity in the secondary auditory cortex, combined with an increase in firing rate for the external nucleus of the inferior colliculus in cats after noise exposure. Salvi, Hamernik,

and Henderson (1978) observed strongly decreased in the dorsal cochlear nucleus in characteristic frequency region with an elevated threshold in chinchillas exposed to an 86 dB SPL, 4kHz noise band for 4 days. The effect tinnitus inducing agents such as noise and ototoxic drugs (salicylate and quinine) have been demonstrated in animal studies on the non-classical pathway (extralemniscal pathway) in changing spontaneous firing rates of the structures in the non-classical pathway. Such changes in the spontaneous firing rate form the basis of the neural substrate of tinnitus. Limbic system was found abnormally activated in some individuals with tinnitus (Lockwood et al., 1998) and such activity in the limbic system may be created by emotional disturbances derived from the experience of tinnitus.

The neural plasticity hypothesis suggests two lines of auditory research. First, animal studies found that noise exposure induces the hearing loss in certain frequencies which leads to a reorganization of tonotopic maps in the primary auditory cortex, in such a way that edge frequencies of the normal hearing region become over-represented in the entire region of those frequencies in the hearing loss (Noreña, 2003). It was suggested that such overrepresentation of tonotopic reorganization might underlie tinnitus because hearing loss is a proposed cause of tinnitus (Eggermont & Roberts, 2004). The second line of research suggests that the neural representation of the primary auditory cortex can be changed over the lifespan by either deafferentation or auditory training (Fritz, Elhilali, & Shamma, 2005; Weinberger, 2007).

Such neural reorganization in both lines of research requires neural synchrony along with neural plasticity. The changes initiated by neural plasticity can be permanent

because of Hebb's principle: neurons that fire together will eventually also connect morphologically together ("wire together") (Møller, 2006). The abnormal synchronous (temporally coupled) firing of the neurons, develop in the auditory cortex when the auditory input from the cochlea is cut off. To explain this neural phenomenon, Rajan and Irvine (1998) proposed the neural synchrony model of tinnitus through the overrepresentation of tonotopicity in the auditory cortex of a cat. Upon hearing loss, the diminished input from the thalamus to cortex reduces excitation and feed-forward inhibition in the neurons that coded for the frequencies in the hearing loss region, resulting in those neurons producing action potentials because of the activation of adjacent unaffected neurons responding to sound frequencies not lost, via input through horizontal connections. Thus, the output of the "affected" neuron remains relatively intact. This result in synchronous firing all along the fiber tracts connecting wide area in the cortex leading to the over-representation of those frequencies not lost in the damage. The synchronous firing exhibits itself in the form of thalamocortical and corticolimbic interaction and may lead to the perception of phantom sound, tinnitus.

Tinnitus and Silence: Short-term Sensory Deprivation and Tinnitus Perception

As noted earlier, approximately 10%–20% of the patients with tinnitus have normal hearing. This suggests that one aspect of the generation of tinnitus may occur when a person with normal hearing experiences prolonged silence. Though very little research has been done on the effect of silence on tinnitus perception and/or severity, the seminal investigation of this phenomenon was the 1953 report by Heller and Bergman (1953). This study was conducted on 80 normally hearing males and females from 10 to

68 years of age without any aural disease and hearing loss. Subjects sat in the soundproof chamber with ambient noise level between 15 dB and 18 dB (re: 0.0002 dynes per cm^2) for five minutes and were instructed to report any sound that might be detected.

Data from normal hearing subjects in this experiment were compared with data obtained on tinnitus perception from 100 hard-of-hearing patients admitted to the clinic. The results in this patient population showed that 75 normal hearing subjects out of 80 (93.75%) reported the perception of sound while sitting in the soundproof chamber. When compared with the hard of hearing subjects, 73 patients out of 100 (73%) reported the perception of tinnitus. The sounds described as “buzz,” “hum,” and “ring” were the most frequently perceived by both groups and comprised at least 50% of the responses of each group. Thus, there appears to be the similarity in the type of tinnitus sound perception associated with hearing loss in hard of hearing patients and type of tinnitus sound perceived in silence by subjects with normal hearing. Heller and Bergman then proposed that perhaps tinnitus is a physiological phenomenon in an intact auditory system that is always masked by ambient noise that usually exceeds 35 dB.

Tucker et al. (2005) conducted a similar experiment on 120 normal-hearing young adults (60 male and 60 females with 40 Caucasians and 20 African Americans in each gender group) to examine the effect of silence on the experience of tinnitus. The aim of the study was to determine whether significant differences exist in tinnitus perception due to gender and race. The results of the study showed no significant gender difference in perception of tinnitus but a significant difference was observed between races with tinnitus perception more common in Caucasian participants (78%) than African

American participants (38%). The most common type of tinnitus sounds perceived was "ring" (57%), "buzz" (21%), "pulse" (22%), "heartbeat" (21%), and "hum" (14%). When compared to Heller and Bergman (1953) study where overall tinnitus perception was 94%, this study reported significantly lower overall tinnitus perception (64%). Unlike the Heller and Bergman study, the silence period was kept for 20 minutes as opposed to 5 minutes. Also, all the subjects had hearing thresholds 20 dB or less for octave frequencies between 250 and 8000 Hz in both ears as opposed to "self" reported normal hearing in all the subjects in Heller and Bergman study. The differences in the results between these two studies might be attributed to the differences in the subject age range, procedures followed, and duration of silence (sound deprivation). Additional studies are needed to explore differences in tinnitus perception due to race.

The study by Tucker et al. (2005) does not support the conclusion proposed by Heller and Bergman (1953) that "tinnitus is a physiological phenomenon in an intact auditory system always masked by ambient noise usually exceeding 35 dB tinnitus" (p. 82). Instead, their study indicated that silence helped to produce temporary tinnitus in normal hearing subjects and that there was a significant difference in tinnitus perception due to race and not gender.

Mason and Brady (2009) studied the effect of short-term complete isolation from sound and vision on the perceptual disturbances in the highly hallucination-prone and non-hallucination prone groups. The result of this study showed that the brief period of sensory deprivation led to significant increase in perceptual disturbances such as anhedonia and paranoia. The hallucination-prone individuals experienced more

perceptual disturbances than non-prone individuals. The perceptual disturbances like anhedonia and paranoia must have the neurological base set in the interaction between visual/auditory nervous system and limbic system (as the sensory deprivation was in visual and auditory senses in the first study). The hallucination-prone and non-prone individuals also may have a "race factor" or "gender" factor contributing to a predisposition to perceptual disturbances because a "race" factor was involved in the tinnitus experience in Tucker's study.

Another short-term sensory deprivation study by Munro, Turtle, and Schaette (2014) showed an increase in loudness rating and over amplification of stimulus-evoked neural activity in the unilateral auditory deprived ear (plugged for 7 days). This is attributed to the gain control mechanism at the lower level of the auditory brainstem. This mechanism increases the neural responses because of sensory deprivation and thus lower sound level required to elicit the stimulus-evoked neural activity (measured by acoustic reflex thresholds) in the sensory deprived ear. The authors concluded that the strength of the excitatory synapses is scaled up and strength of inhibitory synapses is scaled down because of such sensory deprivation.

The findings from studies focused on tinnitus in silence and similar studies on short-term sensory deprivation reveal the need for a more objective approach to assess the auditory system (peripheral and central) involved in tinnitus experience because of silence among normal-hearing listeners. Although neurophysiological aspects of tinnitus provide us with probable structures involved in tinnitus experience resulting from hearing loss and auditory pathological structures, the exact cause of tinnitus experience remains

unknown for normal hearing individuals when silence is a triggering factor. The present study will focus on the assessment of the medial olivocochlear (MOC) reflex pathway. This pathway is well defined and can be assessed acoustically by measuring contralateral suppression of otoacoustic emissions. The projections and connections of and with medial olivocochlear bundle make it potential pathway that may be involved in tinnitus perception. The functional anatomy of the MOC pathway is described in the following section.

Brief Functional Anatomy of Efferent Auditory Pathway

To understand suppression of the otoacoustic emissions, it is important to review the functional anatomy of the efferent auditory system that starts in the cortex and terminates in the cochlea, the olivocochlear bundle (OCB) originates in the brainstem and terminates in the cochlea (Guinan, 2006). The functional anatomy of the auditory efferent system is shown in Figure 2.

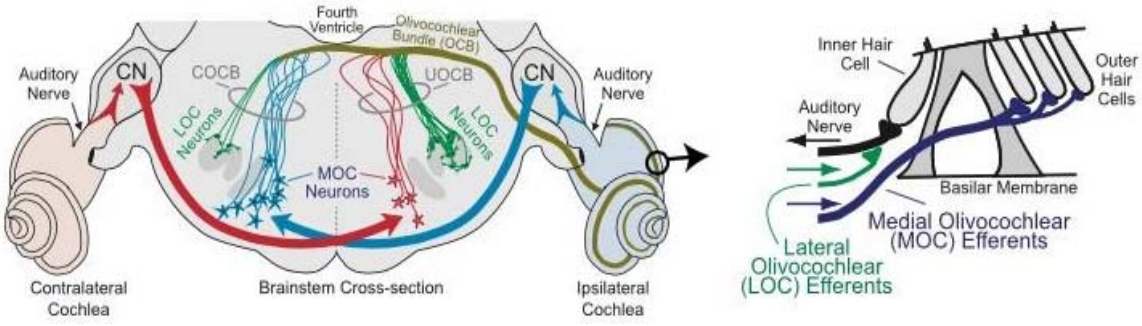

Figure 2. The Functional Anatomy of the Efferent Auditory System (Olivocochlear Pathway). Adapted from "Olivocochlear Efferents: Anatomy, Physiology, Function, and the Measurement of Efferent Effects in Humans," by J. J. Guinan, 2006, *Ear and Hearing*, *27*(6), 589-607. Copyright 2006 by the Wolters Kluwer Health, Inc. Adapted with Permission.

The OCB consists of both lateral (L) and medial (M) olivocochlear (OC) fibers, which originate in lateral and medial olivocochlear nuclei, respectively. Each cochlea receives both crossed and uncrossed lateral olivocochlear bundle and medial olivocochlear bundle fibers. As shown in right side of Figure 2, the thick, myelinated medial olivocochlear bundle fibers that project predominantly to the contralateral cochlea and terminate at the base of the outer hair cell (OHC) and thin unmyelinated lateral olivocochlear bundle fibers terminates on the dendrites of the auditory nerve fibers (Guinan, 2006). Animal studies have shown that medial olivocochlear fibers can be electrically and acoustically stimulated. In contrast, the electrical and acoustical stimulation of lateral olivocochlear fibers is limited and no conclusion has been made if lateral olivocochlear fibers show any activity after electrical stimulation or whether or not they can be acoustically stimulated.

There are three ways to record efferent olivocochlear bundle stimulation: a) Ipsilateral acoustic stimulation: acoustic stimulation in the same ear in which measurement of the modulation of otoacoustic emissions is being done b) Contralateral acoustic stimulation: acoustic stimulation in the opposite ear c) Binaural acoustic stimulation: Both ears (the ear in which modulation of otoacoustic emissions is being measured and the opposite ear) are stimulated simultaneously.

Suppression of Otoacoustic Emissions (OAEs) in Population with Normal Hearing Sensitivity

The effects of contralateral and ipsilateral competing stimuli on OAEs have been studied using auditory stimulation in human subjects and artificial electrical stimulation

in animal subjects. The physiological effects of such stimulation were manifested in the suppression of stimulated and spontaneous otoacoustic emissions through the auditory efferent system, specifically the medial olivocochlear efferent in the brainstem (Guinan, 1996; Harris and Glattke, 1992). The functional role of the auditory efferent system is not fully understood but some studies showed its importance in protection from acoustic trauma (Rajan, 2000; Maison & Liberman, 2000) and improved speech perception in noise (Kumar & Vanaja, 2004). Thus, research in the auditory efferent system has valuable clinical applications.

To understand the suppression of otoacoustic emissions, different otoacoustic emissions are discussed in following sections.

Otoacoustic Emissions (OAEs)

Otoacoustic emissions are the echo of sounds generated in the cochlea by the movement of the sensory hair cells (Outer hair cells) in response to a stimulus (Kemp, 2002). The energetic motion of the outer hair cells due to its characteristic "electromotility" gives rise to cochlear amplification and as a result, some energy escapes to the oval window in the form of reverse traveling wave measured as otoacoustic emissions. Thus, otoacoustic emissions are the sign of healthy cochlear function and provide simple, efficient, and objective measures to assess the cochlear function (Kemp, 2002). The otoacoustic emissions, as a research tool, provide a non-invasive tool not only for the assessment of cochlear function (Kemp, 2002) but also for the assessment of efferent auditory pathway (Giraud, Collet, Chéry-Croze, Magnan, & Chays, 1995).

Classification of Otoacoustic Emissions

Otoacoustic emissions (OAEs) have been classified based on two viewpoints. The first is the traditional classification based on the types of stimulus used to elicit and record the otoacoustic emissions. The second is based on the physiological mechanism involved in their creation (Kemp & Brown, 1983; Knight & Kemp, 2000, 2001). For this literature review, the first classification system based on the type of stimulus or no stimulus will be used.

Spontaneous otoacoustic emissions. Spontaneous otoacoustic emissions (SOAEs) are low tonal signals produced in the cochlea without any external auditory stimulation (Kemp, 2002). The structural irregularities in the cochlea are the probable cause of generating spontaneous otoacoustic emissions (Kemp, 1986; Manley, 1993). These irregularities set up the reverse travelling wave along the basilar membrane eventually recorded as spontaneous otoacoustic emissions in the ear canal (Kemp, 1986). The spontaneous otoacoustic emissions are classified as pure reflection emissions because they are emitted from cochlear standing-wave resonances (Shera, 2003, 2004). Shera (2003) suggested that internal physiological or even environmental noises act as a source of vibrational energy to the basilar membrane initiating forward traveling waves. These forward traveling waves are then reflected by random roughness and minor irregularities present along the basilar membrane that set up a reverse traveling wave propagating towards the oval window. These reverse traveling waves, in turn, get reflected from the oval window (the boundary between inner and middle ear impedance mismatch) and travel near their characteristic frequency regions. The “in phase”

interaction between forward and reverse traveling waves in many places create a standing wave that leaks out as spontaneous otoacoustic emissions. The amplitude of the reverse traveling wave increases at the places where standing waves are created. This happens because of the multiple reflections of the standing waves from the irregularities along the cochlear partition. Eventually some portion of this increased amplitude leaks as a spontaneous otoacoustic emissions (Shera, 2003).

In initial years, after spontaneous otoacoustic emissions discovery, technical limitations in the instrumentations made it difficult to record spontaneous otoacoustic emissions frequently in adults, therefore the prevalence of spontaneous otoacoustic emissions in adults was less than 40%. However, with the subsequent invention of new-sophisticated instrumentation, the prevalence has reached to approximately 80% (Kuroda, 2007; Strickland, 1985). Bilger, Matthies, Hammel, and Demorest (1990) and Penner, Glotzbach, and Huang (1993) have reported that the right ear has more frequency of SOAEs occurrence than left. The female to male ratio of spontaneous otoacoustic emissions occurrence is approximately 2:1 (Bilger et al., 1990; Martin, Probst, & Lonsbury-Martin, 1990). In adults, SOAEs is mostly measured in the frequency region between 1000 and 2000 Hz. In infants and newborns, the range is 2500-5000 Hz (Morlet et al., 1995). The spontaneous otoacoustic emissions can be up to -15 to 10 dB. The spontaneous otoacoustic emissions are affected by ototoxic drugs, which can affect the cochlear amplification due to the damage in the outer hair cell (Kuroda, Chida, Kashiwamura, Matumura, & Fukuda, 2008). Thus, the presence of spontaneous otoacoustic emissions indicates normal hearing functioning and healthy cochlea.

In contrast, animal studies in chinchilla reported initiation of spontaneous otoacoustic emissions after noise exposure (Clark, Kim, Zurek, & Bohne, 1984) and high amplitude spontaneous otoacoustic emissions were recorded from the frequency region where cochlear damage was present (Nuttall et al., 2004). Such relation of spontaneous otoacoustic emissions and cochlear damage might support the reflection phenomenon. The structural damage creates the irregularities in the cochlea. As mentioned earlier, cochlear irregularities are responsible for the generation of spontaneous otoacoustic emissions. Thus, the cochlear damage becomes the source of spontaneous otoacoustic emissions. In select patients, the frequency of perceived tinnitus can coincide with a patient's recorded spontaneous otoacoustic emissions frequencies; however, this is not true for every tinnitus patient, and generally, the relationship between tinnitus and spontaneous otoacoustic emissions has not been found to be statistically significant (Ceranic, Prasher, Raglan, & Luxon, 1998).

Transient evoked otoacoustic emissions (TEOAEs). Transient otoacoustic emissions (TEOAEs) are the acoustic energy emitted by an active process in the cochlea in response to brief broadband click stimuli (Hall, 2000). The transient otoacoustic emissions are nonlinear and non-stationary in nature. The transient otoacoustic emissions consist of different frequency components at different moments of time and its response amplitude grows nonlinearly with an increase in the stimulus intensity (Kemp, 1978). Click stimuli are comprised by a set of four stimuli presentations with the first three in one phase and the fourth in opposite phase of the first three but with an amplitude three

times greater than the first three. The next stimulus sequence of clicks would be with reverse polarities for all four stimuli.

The response to these four stimuli would have linear components (components that follow the stimuli exactly) and nonlinear components (TEOAEs). Because the polarity of forth stimuli is exactly opposite and the power is equal to the sum of the power of the first three stimuli, the sum of the linear components will be zero leaving the nonlinear components for recording and analysis. These nonlinear components are transformed into the frequency domain after eliminating the first few milliseconds of data to avoid the contribution of stimulus artifacts in the average response waveform. These nonlinear components are displayed as the transient otoacoustic emissions.

Effect of gender on TEOAE. Gender differences can be reported in the human peripheral and central auditory nervous system. McFadden (1998) summarized various auditory system differences between males and females. Male heads, pinna, external ear canals, and middle-ear volumes are larger than females. Males have a longer cochlea than females. These differences contribute significantly to the differences in the TEOAEs between males and females. Females have significantly higher amplitude and reproducibility in TEOAE values than males (McFadden, 1998; Robinette, 1992; Shahnaz, 2008).

Characteristic of a TEOAE response waveform. Figure 3 shows the transient otoacoustic emissions response displayed on the Otodynamics Ltd. ILOV6 292-I instrument analysis window. The “Stimulus, Response” waveform and OAE response

window are the most common aspects of the transient otoacoustic emissions displayed in commercially available instruments.

1. *Demographic data:* The left column of the screen shows the demographic data of the subjects such as name, date of birth, gender etc.
2. *Stimulus:* The stimulus panel shows the biphasic click stimulus waveform because of 80 μs electric pulse applied to the transducer. The x-axis displays the time recorded after the click presentation in milliseconds with a window up to five milliseconds. The y-axis displays amplitude scale of the click stimulus in pascals (Pa), which is related to the intensity of the click. The amplitude of stimulus is slightly less than 0.3 Pa (0.3 Pa is equivalent to 83.5 dB SPL). The green circle in the stimulus window is the traffic light indicator. It represents the stability figure. It turns green when the stability figure is over 90, orange for over 70 and red for below 70.
3. *Response waveform:* The response waveform panel shows the overlapping of time-averaged response from the two memory locations (each one gets half of the data points) sampled for 20-ms. Appropriate overlapping between two waveforms is displayed here and indicated waveform reproducibility. The amplitude of the response waveform is set at the 0.5 mPa. The response waveform is time-averaged waveform sampled for 20 ms period following the transient stimulus. First 2-3 ms shows straight line because it is the time through which stimulus is extended. After the stimulus stops, the software starts analyzing the response waveform.

4. *OAE response window:* The raw transient otoacoustic emissions response is analyzed using an FFT, and the half-octave bands for the transient otoacoustic emissions response (Blue bars) with noise energy (Red bar) is displayed as a histogram. This is the Fast Fourier Analysis of the transient otoacoustic emissions response waveform. The transient otoacoustic emissions responses are measured across frequency range 1 kHz – 8 kHz and are recorded in dBSPL.

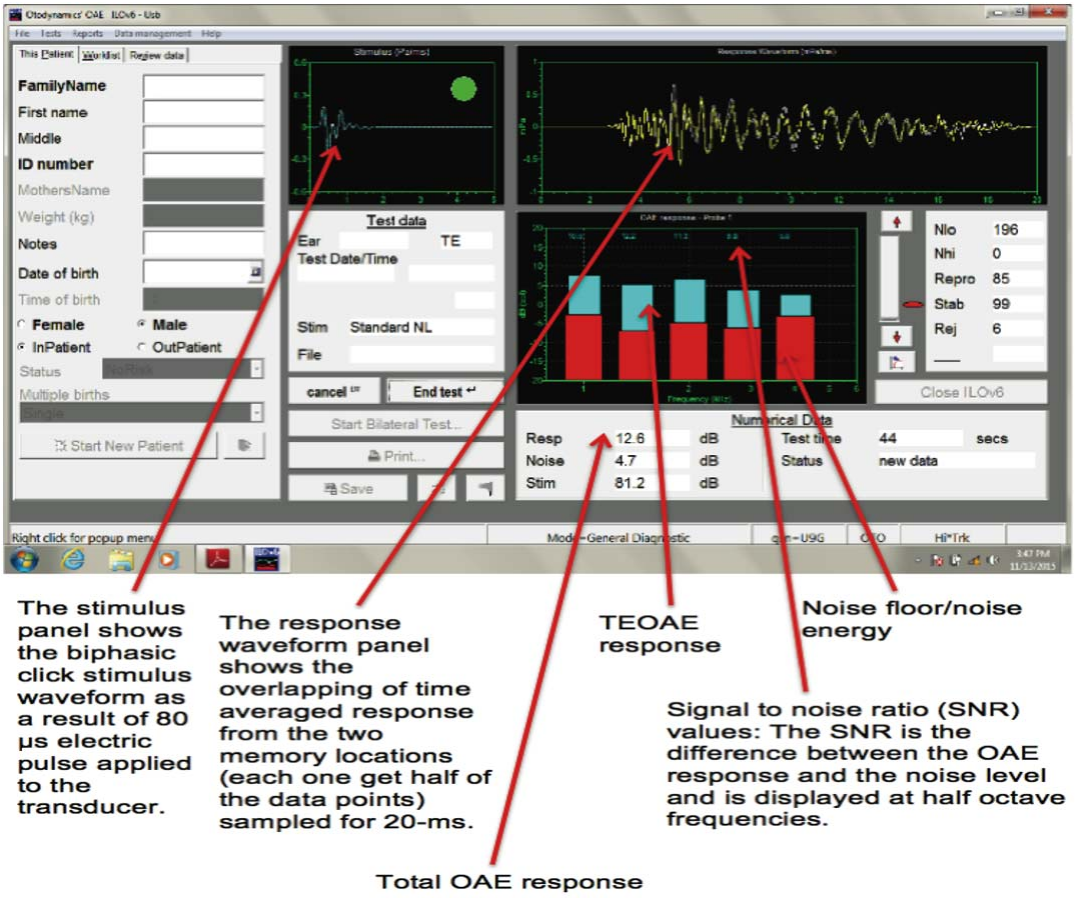

Figure 3. A TEOAE Otodynamics Ltd. ILOv6 OAE System Showing the Transient Otoacoustic Emissions Response and Analysis Screen. The Transient Otoacoustic Emissions Response Obtained from a Young Adult Male is Shown with Various Stimulus Characteristics.

Distortion product otoacoustic emissions (DPOAEs). The DPOAEs are the responses from the cochlea because of an intermodulation distortion initiated by the nonlinear aspects of cochlear processing. An introduction of two simultaneous, pure-tone stimuli or primary tones close in frequency into the external auditory canal creates such distortion (Kemp, 1979). The regional mechanical nonlinearities cause reverse propagation of distortion energy that can be recorded in the external auditory canal. A stimulus of two primary tones f1 (low frequency) with its level as L_1 and f2 (f2>f1) with its levels as L_2 and ratio of 1.22 (i.e., f2/f1=1.22) are introduced together, and a resulting distortion product 2f1-f2 is measured. The 2f1-f2 DPOAEs is commonly recorded because it is the largest measurable DPOAE in human ears.

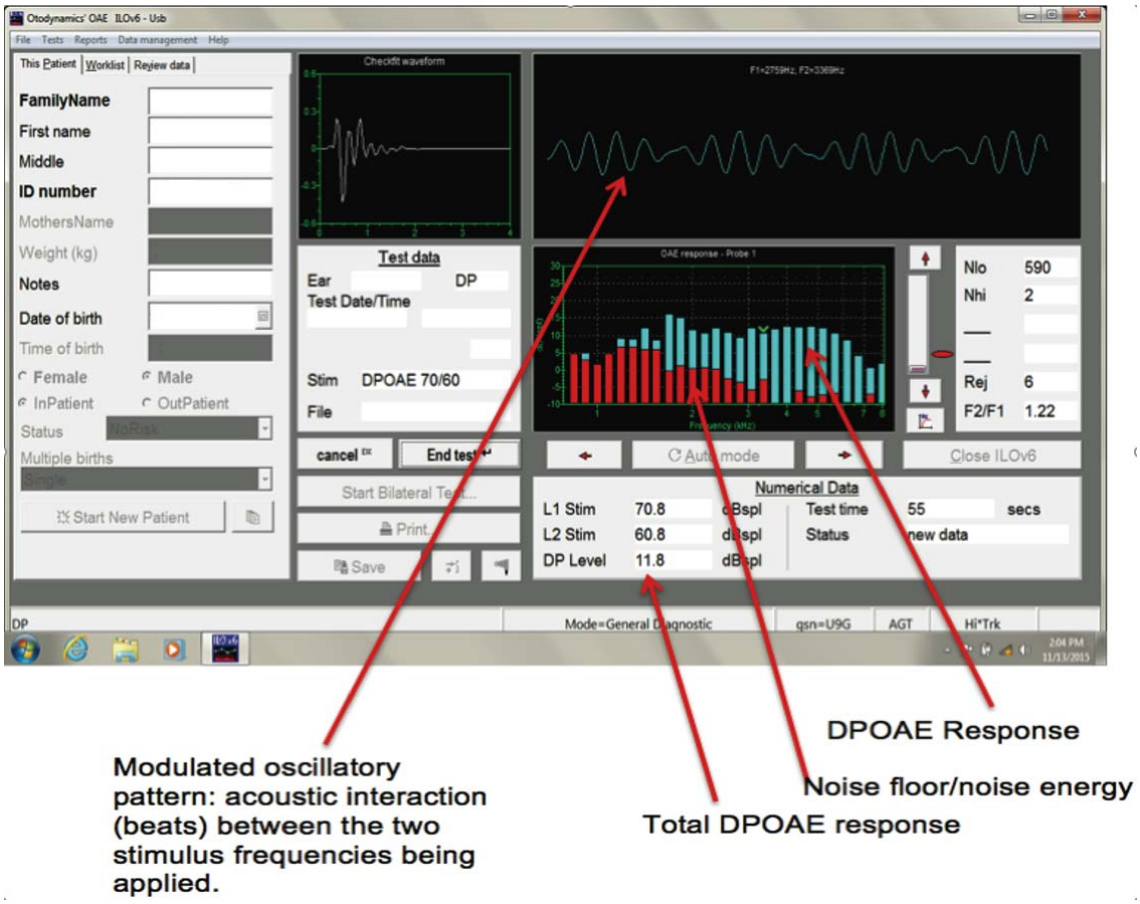

Figure 4. A DPOAE Otodynamics Ltd. ILOv6 OAE System Showing DPOAE Response and Analysis Screen. The DPOAE Response (The OAE is Shown in the Blue Portion of Bars. The Red Portion is Noise Floor) Obtained from a Young Adult Male is Shown with Various Stimulus Characteristics. The Screen Data Fields *Nlo, Nhi* and, *Rej* Have the Same Interpretation Explained in the Previous Section about TEOAEs. Stim: in This Figure Shows L_1=70 dB SPL and L_2=60 dB SPL Protocol Commonly Used. The *F2/F1* Ratio is 1.22 for Maximum Overlap between Two Primaries and Robust $2f_1$-f_2 DPOAE Recording. *DP Level*: Total DP Power in dB SPL. *L1 and L2 stim*: the DP Stimulus Levels Used in dB SPL.

Stimulation of OAEs

Altered or abnormal efferent auditory pathway function has been observed in tinnitus patients using both contralateral suppression of Distortion product Otoacoustic emission (Chéry-Croze et al., 1993) and Transient evoked Otoacoustic emissions (Geven

et al., 2012; Lalaki et al., 2011). Therefore, recording of contralateral suppression of otoacoustic emissions in tinnitus perception in silence can be a useful tool to assess the medial olivocochlear function and its relationship to tinnitus perception.

Ipsilateral Acoustic Stimulation

In the ipsilateral acoustic stimulation, the acoustic stimulus crosses midline from the stimulated ear (ipsilateral ear) via afferent neurons to stimulate efferent neurons of the opposite side olivocochlear bundle and then these efferent neurons from the opposite side cross back over to have their influence on the ipsilateral stimulated cochlea. This pathway involves crossed olivocochlear bundle (COCB) (see Figure 2).

Contralateral Acoustic Stimulation

Unlike ipsilateral stimulation, contralateral acoustic stimulation crosses over to the opposite side via afferent but the efferent effect is carried out by the uncrossed olivocochlear bundle (UOCB) (Guinan, 2006). This means stimulating one ear and measuring the effect in the opposite ear (see Figure 2), and in binaural stimulation, both uncrossed olivocochlear bundle and crossed olivocochlear bundle are stimulated (Guinan, 2006).

Suppression of Transient Evoked OAEs (TEOAEs)

Suppression of TEOAEs can be recorded using ipsilateral, contralateral, or binaural acoustic stimulation (Dhar & Hall, 2012). In ipsilateral suppression of TEOAE, the undesirable interaction between emission evoking stimulus and suppressor stimulus makes this method difficult to record genuine results. Therefore, a forward masking paradigm in which the suppressor precedes the stimulus is used to record ipsilateral

suppression of TEOAEs (Tavartkiladze, Frolenkov, Kruglov, & Artamasov, 1994). The most commonly used method to measure suppression of TEOAEs is the contralateral suppression mode (contralateral acoustic stimulation) in which continuous noise is presented to the contralateral ear during the time that OAEs are recorded.

The consistent decrease of 1-4 dB is seen in the overall emission amplitude (Berlin et al., 1993, Berlin, Hood, Hurley, & Wen, 1994). The greatest amount of suppression for the contralateral continuous noise was found for lower intensities 55 and 60 dB peak SPL as opposed to higher intensities (Hood, Berlin, Hurley, Cecola, & Bell, 1996). Noise is a more effective stimulus than pure tones as the suppressor. Broadband noise has been found to be most effective suppressor than narrowband noise and tones when click stimulus was used for TEOAE emissions (Berlin et al., 1993). The white noise of 60-65 dB is recommended. In addition, the duration of suppressor up to 400 ms with its continuous contralateral presentation during recording TEOAEs was found to have a greater amount of inhibition. The studies have reported that the TEOAEs suppression value varies from less than 1 dB to several dBs (Muchnik et al., 2004; Prasher, Ryan & Luxon, 1994; Veuillet, Collet, & Duclaux, 1991). Muchnik et al. (2004) reported a mean of 1.57 dB (*SD*=0.64) in right ear and mean of 1.61 dB (*SD*=0.68) in the left ear. The means values in other studies ranged between 0.8 to 2 dB (Burguetti & Carvallo, 2008; Kumar & Vanaja, 2004). The difference in the mean value could be attributed to changes in the protocol and inter-subject variability in modulatory effect on the cochlear gain (De Boer, Thornton, & Krumbholz, 2011). The individual differences in the level of TEOAEs may also affect the magnitude of suppression (De Ceulaer et al.,

2001). Because of these variations, it is difficult to arrive at a specific and uniform decision criterion to define the presence or absence of suppression. However, a few investigators have reported criteria for stating decisions. Majorities of the studies have used 0.6 dB as the decision criterion (Muchnick et al., 2004; Prasher et al., 1994).

See Figure 8 in Appendix D for TEOAE waveform before suppression and after suppression.

Tinnitus and Suppression of Otoacoustic Emissions

Abnormal distortion product otoacoustic emissions and transient otoacoustic emissions findings in a person with tinnitus suggest that peripheral pathological changes, such as abnormal outer hair cell function, may contribute to the generation of tinnitus. There have been several previous studies conducted to explore the involvement of medial olivocochlear (efferent control) in the subjects with tinnitus using otoacoustic emission assessment. A smaller suppression effect in transient otoacoustic emission (with the use of contralateral broadband noise stimulation) was observed ipsilateral to the ear of tinnitus perception (where the tinnitus was perceived) in the normal hearing subjects with unilateral tinnitus (Veuillet et al., 1991). A subsequent study by Chéry-Croze et al. (1993) observed variation in medial olivocochlear function in all of their 16 bilateral tinnitus patients with normal hearing sensitivity and 50% of their unilateral tinnitus patients with normal hearing sensitivity. The suppression was tested using contralateral suppression of TEOAEs and DPOAEs. This alteration in medial olivocochlear was the manifestation of either abnormally small or no suppression using contralateral noise and enhancement in distortion product otoacoustic emission amplitude with contralateral stimulation. In

addition, distortion product otoacoustic emission findings showed medial olivocochlear dysfunction in the frequency region of the tinnitus.

Riga, Papadas, Werner, and Dalchow (2007) experimented with suppression of distortion product otoacoustic emissions in 18 normal hearing adults (seven men, 11 women) with acute tinnitus. Three subjects had bilateral tinnitus. Results showed a lack of statistically significant distortion product otoacoustic emission amplitude suppression after application of contralateral white noise in either ear (with or without tinnitus) in normal hearing adults with acute tinnitus. Additionally, they observed an enhancement of distortion product otoacoustic emission amplitude in some patients after application of contralateral noise. Conversely, they report statistically significant contralateral suppression of distortion product otoacoustic emission amplitude in their control group matched with subjects with respect to sex, ear side, and age distribution. Thus, the less effective functioning of the cochlear efferent system seemed to be indicated in adults with normal hearing who had acute tinnitus.

The findings from the distortion product otoacoustic emission suppression studies need to be analyzed with caution. The distortion product otoacoustic emission consists of two components (place fixed waveform and wave fixed waveform) and these two sources interfere and make the medial olivocochlear reflex effect on distortion product otoacoustic emission very complex. Sometimes it may increase the distortion product otoacoustic emission (Müller, Janssen, Heppelmann, & Wagner, 2005; Wagner, Heppelmann, Müller, Janssen, & Zenner, 2007). The increase in the distortion product otoacoustic emission findings after medial olivocochlear reflex activation can be

explained by the phase relationship between two sources of distortion product otoacoustic emissions. If the two components of distortion product otoacoustic emissions normally cancel, and medial olivocochlear stimulation inhibits one component (source) more than the other, this inhibition reduces the cancellation and increases the distortion product otoacoustic emission. Thus, the relative phases of the two-distortion product otoacoustic emission components greatly influences the distortion product otoacoustic emission change measures in the ear canal.

Such phase relationship is not related to the medial olivocochlear effect but can strongly influence the result of the medial olivocochlear reflex action. Thus, change in distortion product otoacoustic emission amplitude is not the accurate measure of medial olivocochlear reflex effect. Therefore, in this study, contralateral suppression of transient otoacoustic emissions is selected as the tool for recording any change in the transient otoacoustic emission because of medial olivocochlear reflex activation due to contralateral white noise.

Summary of Literature and Research Hypotheses

A review of the literature has shown that (a) tinnitus can be perceived after a period of silence, and (b) suppression of otoacoustic emissions is abnormal (lacking) in patients with chronic tinnitus. Research is needed to further understand the effect of silence on temporary and chronic tinnitus and the role that the efferent auditory system plays in tinnitus perception. In addition, research is needed to determine if an abnormal suppression of otoacoustic emissions will appear in normal hearing subjects after a period of silence in which the perception of tinnitus may or may not occur and to document the

magnitude of suppression. Thus, although contralateral suppression has been researched over two decades, there is no consensus on the exact protocol to be used for the magnitude of suppression observed in persons with normal hearing after a period of silence.

The purpose of this study is to assess the role of the efferent auditory pathway (medial olivocochlear pathway) in the perception of tinnitus in silence using the measure of contralateral suppression of transient evoked otoacoustic emission. This study will explore the physiology of connecting neural pathway between the afferent auditory pathway and medial olivocochlear efferent, medial olivocochlear efferent and outer hair cell and outer hair cell and afferent pathway (see Figure 5).

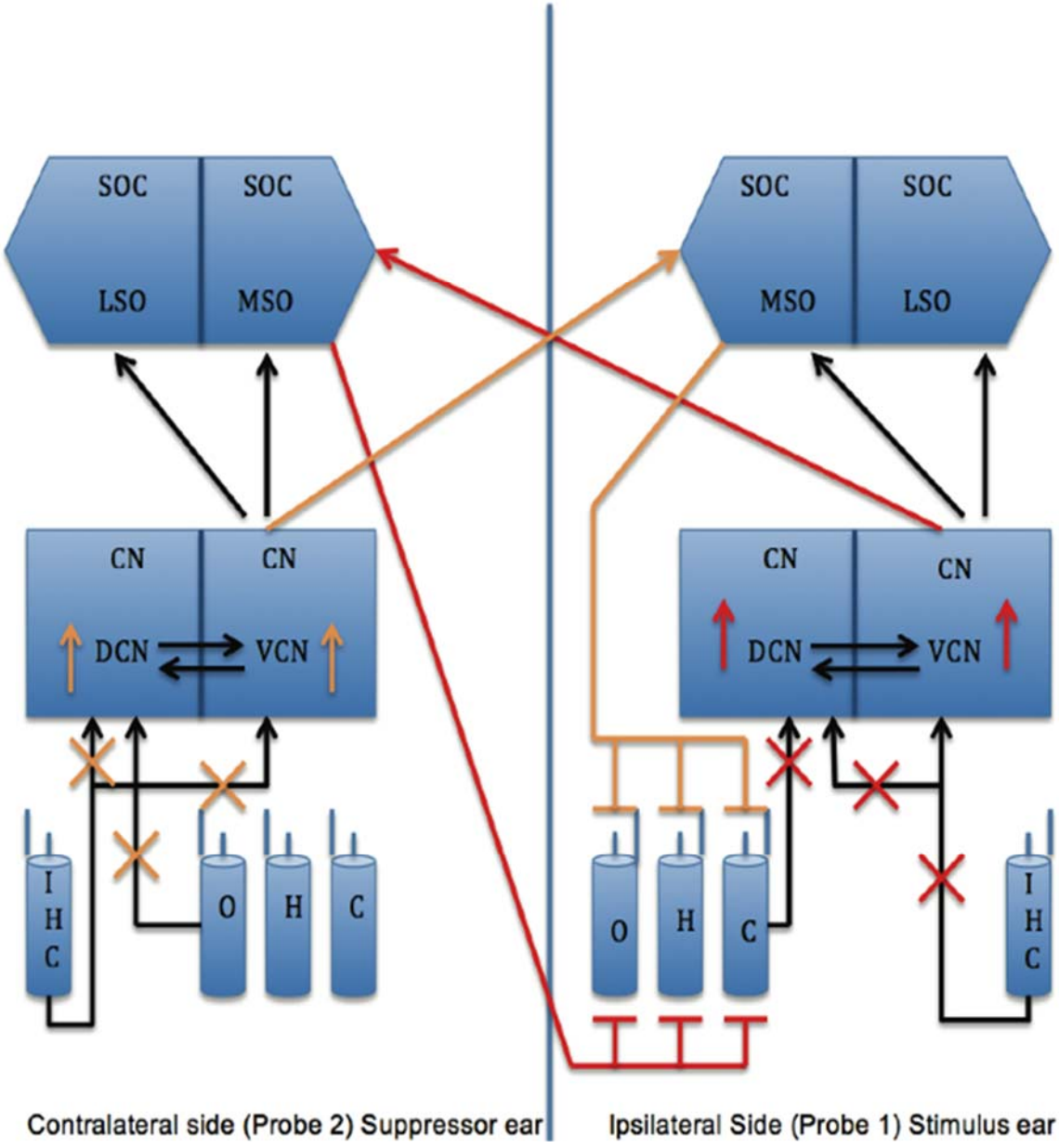

Figure 5. Theoretical Model for This Study. The Cross Marks (Red and Orange) Shows Lack of Auditory Input Due to Silence in a Sound Booth. The Upward Arrows (Red and Orange) in Cochlear Nucleus (CN) Show Hyperactivity Due to Lack of Inhibitory Input from the Periphery. The Red and Orange Pathway Shows the Inhibitory Input to the Outer Hair Cells (OHC) Due to Hyperactivity in the CN. Identical Phenomenon and Pathways are Hypothesized for the Contralateral Ear.

Research Hypotheses

Hypothesis 1: The total transient otoacoustic emission amplitude values will be statistically significantly decreased after a period of 10 minutes of silence in test ear (right ear).

Rationale for Hypothesis 1: Lack of peripheral auditory input due to noise-induced hearing loss causes hyperactivity in the cochlear nucleus. Here, it was hypothesized that the lack of peripheral auditory input due to silence would cause the same hyperactivity in the cochlear nucleus. This hyperactivity in the cochlear nucleus after the silence period would then activate the medial olivocochlear neurons and in turn produce more transient otoacoustic emission suppression through uncrossed medial olivocochlear neurons (UCMOC) innervated by ipsilateral interneurons or through crossed medial olivocochlear neurons (CMOC) innervated by contralateral interneurons, and as a result total transient otoacoustic emission amplitude would be decreased significantly.

Hypothesis 2: The transient otoacoustic emission suppression amplitude will be significantly increased after a period of 10 minutes silence in test ear (right ear).

Rationale for Hypothesis 2: Lack of peripheral auditory input due to silence would cause hyperactivity in the cochlear nucleus. This hyperactivity in the cochlear nucleus would then hyperactivate the medial olivocochlear neurons and in turn, would produce more transient otoacoustic suppression in the test ear (right ear).

Hypothesis 3: Participants perceiving tinnitus after 10 minutes of silence will have a greater amount of TEOAE suppression in post-silent measurement than the participants without the perception of tinnitus.

Rationale for Hypothesis 3: Since tinnitus has been linked to noise-induced hyperactivity in the cochlear nucleus due to lack of peripheral inhibition, in this study the participants perceiving tinnitus would be expected to have similar changes in the cochlear nucleus after a silent period. Therefore, their tinnitus would be linked to increased suppression of transient evoked otoacoustic emission post-silent period.

CHAPTER III

METHODS

The objective of this study was to assess the function of Medial Olivocochlear reflex pathway (MOC) before and after the period of brief silence and its possible role in the perception of tinnitus in silence. The rationale for the study was that the contralateral suppression of transient otoacoustic emissions before and after the period of silence gives the insight into the function of the medial olivocochlear reflex pathway in the perception of tinnitus in silence.

Subjects

The participant pool consisted of 58 males. The age range criterion was 18-35 years. The pool consisted of 40 Asians, 14 Caucasians, and 4 African Americans.

Participants met the inclusion criterion only if they had normal hearing thresholds of < or equal to 25 dB HL at octave frequencies from 250 Hz to 8000 Hz and also at 3000 & 6000 Hz. Participants with no abnormalities or pathologies in the ear canal, including wax, as seen by looking in the ear with an Otoscope were included in the study. Additionally, each participant had normal middle ear function as evidenced by otoscopic examination and tympanometry (Static compliance between +100 daPa and -100 daPa, 0.33 cc > middle ear compliance < 1.75 cc). Also, all participants did not have any history of hearing loss, chronic tinnitus, head trauma, middle ear pathology, ear surgery,

neurological disease, and prolonged history of noise exposure or trauma (see Appendix B: Case History Questionnaire).

Recruitment Method

The participants for this study were recruited in following ways:

1. Subjects were recruited individually. See Appendix G for Recruitment Script (In-Person).
2. Flyers were distributed in the UNCG classes with the permission of respective instructors. Interested students contacted investigator through email or phone. See Appendix F for Recruitment Flyer.
3. The investigator sent an email to the instructor along with the faculty letter. See Appendix H for Faculty Letter. The respective instructor forwarded the email to the students with the faculty letter script. Investigator responded by email to those students who contacted him as of result of the recruitment email sent to them by their instructor.

Data Collection Procedure

The Institutional Review Board for the protection of human research participants at the University of North Carolina at Greensboro approved this study. Each participant signed IRB approved (stamped) informed consent form before participating in the study (see Appendix E for Informed Consent Form). The participants recruited for this study were instructed to avoid exposure to loud sounds such as MP3 player music, vacuum cleaners, motorbikes, lawn mowers and so forth at least 12 hours before testing. The data

was collected in the sound-treated booth meeting ANSI standards in the Ferguson Building, Room 327-A, UNCG.

Instrumentation and Calibration

Auditory hearing sensitivity was assessed using Audiology clinical equipment housed in the UNCG Speech and Hearing Center on the third floor of the Ferguson Building. This equipment included the Grason-Stadler (GSI) 61 clinical audiometer and Eartone 3-A inserts. GSI TympStar Middle Ear Analyzer was used to assess middle ear function. Otodynamics Echoport ILOV6 292-I instrument was used to measure transient otoacoustic emissions (TEOAEs) and subsequent contralateral suppression of transient otoacoustic emissions. All the mentioned equipment was calibrated on February 4th, 2016.

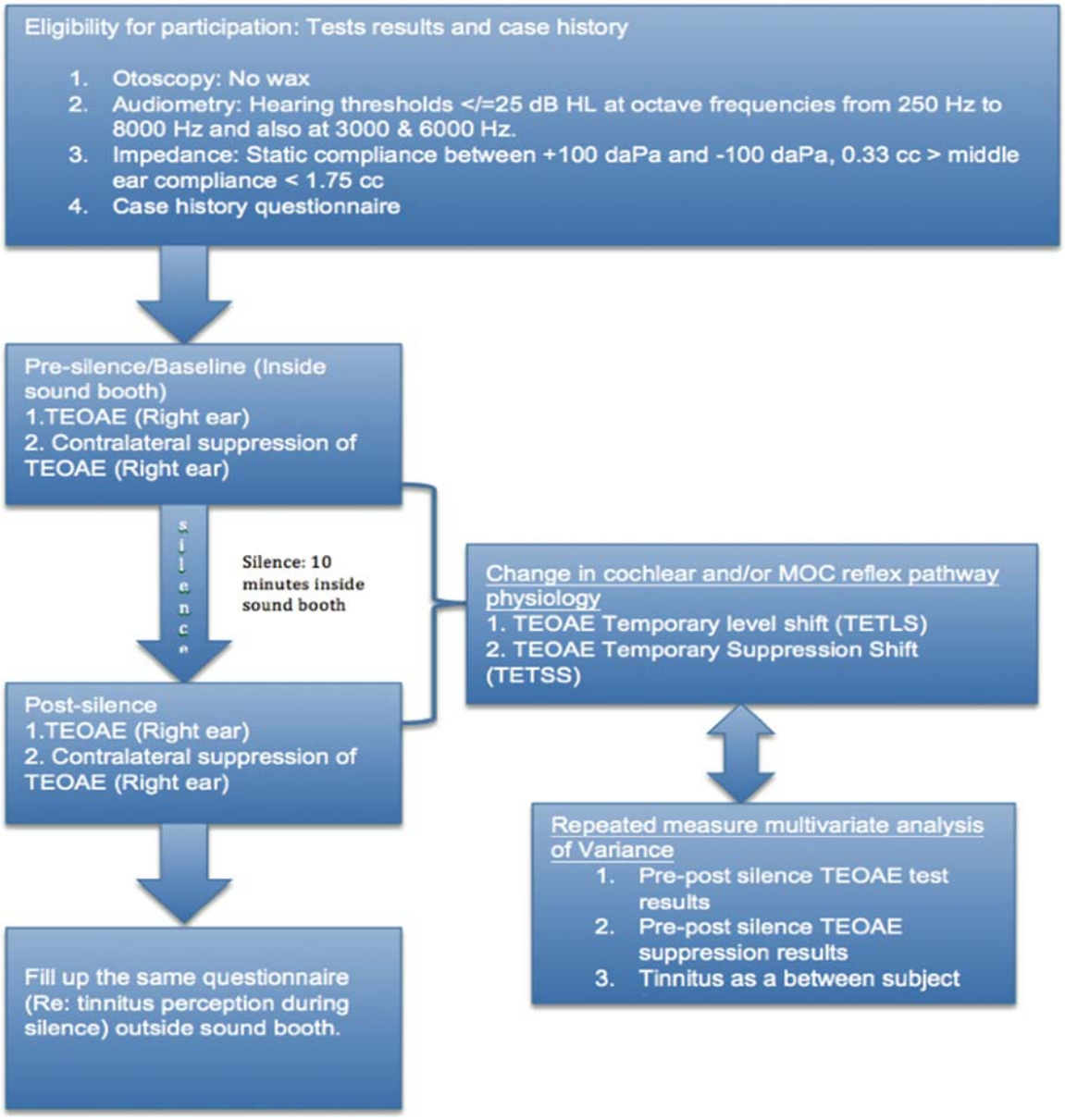

Figure 6. Schematic Diagram of the Research Method. This Figure Shows the Schematic Diagram of Research Design and Relevant Statistical Analysis Tests.

Procedure

Each participant was instructed to sit in an upright comfortable position on a chair inside the sound booth.

Case History Questionnaire

Participants completed a paper case history. The case history questionnaire contains questions about the hearing status and neurological status. (See Appendix B for questions).

Audiometry

The participants were tested in a sound booth for peripheral hearing sensitivity at 250, 500, 1000, 2000, 3000, 4000, 6000, and 8000 Hz frequency to ensure normal hearing sensitivity using ASHA guidelines (2005). The Grason-Stadler (GSI) 61 clinical audiometer and Eartone 3-A inserts were used to assess peripheral hearing sensitivity (pure tone air conduction thresholds).

Assessment of Middle Ear Function with Tympanometry

Tympanometry was performed inside the sound booth to assess normal middle ear function. GSI TympStar Middle Ear Analyzer (calibrated on February 4, 2016) was used to assess middle ear function.

Inclusion in the Study

If the participant's middle ear function and hearing thresholds were normal, the participant was included in the study and the transient evoked otoacoustic emissions recordings and silence experiments were conducted. If the participant's middle ear function or hearing thresholds were not within normal limits, the participant was

excluded from the study and was referred for follow-up testing with a doctor and/or audiologist.

Simultaneous Transient Evoked Otoacoustic Emissions (TEOAE) and TEOAE Suppression Testing and Silence Exposures

Figure 7 illustrates the simultaneous *transient evoked otoacoustic emissions* and TEOAE suppression recording.

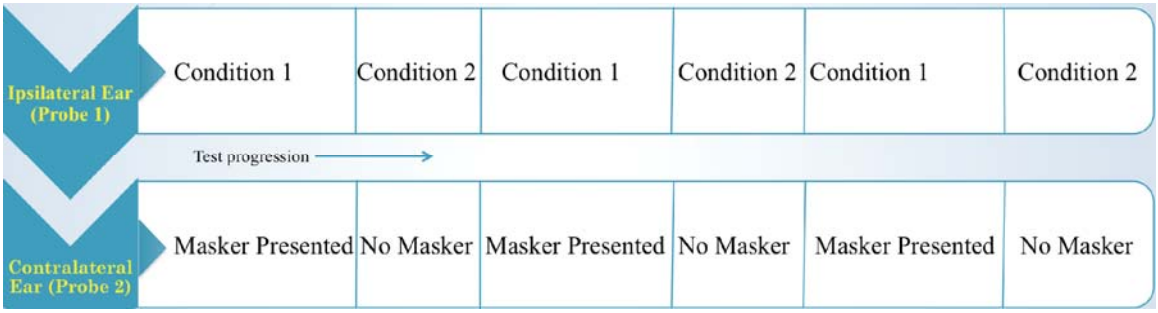

Figure 7. Continuous Contralateral Suppressor Noise Method. Probe 1, Test (Ipsilateral) Ear: Click Stimulus is Presented. Probe 2, Contralateral Ear: Suppressor Broadband Noise is Presented. In "Masker ON" Condition, the TEOAEs are Recorded with Suppressor Noise (Contralateral Suppression of TEOAEs). In "Masker OFF" Condition, TEOAEs are Recorded without Suppression. These Two Conditions are Interleaved for Three Times to Record Reliable TEOAEs with and without Suppression.

Continuous Contralateral Noise Suppressor Paradigm

TEOAEs and contralateral suppression effect of TEOAEs were measured using a continuous contralateral suppressor noise paradigm. This paradigm was an advanced binaural OAE measurement available in ILOV6 292-I OAE instrument (Calibrated on 02/04/2016). In this paradigm, two separate TEOAE recording conditions were recorded simultaneously. One TEOAE recording was done with a suppressor (masker) noise being presented to the opposite ear and the other recording was made from the ipsilateral ear

with no suppressor. These two simultaneous recording conditions were interleaved during stimulus presentations of contralateral noise so the effect of any slow changes in recording conditions (for example changes in probe fit) was minimized (Berlin et al., 1993; Collet et al., 1990; Ryan, Kemp, & Hinchcliffe, 1991).

TEOAE and TEOAE Suppression Recording Parameters

Three repetitions of each condition were performed with 100 clicks in each condition for better stimulus stability and response reproducibility. Then those three TEOAE recordings were averaged together into the final TEOAE and TEOAE suppression recording. The TEOAE responses and contralateral suppression responses were automatically accepted only when the stimulus stability exceeded 80% and the reproducibility of the emissions exceeded 70% (Hood et al., 1996). The recommended stimulus intensity for the click stimulus in linear mode (Robinette & Glattke, 2007) for contralateral suppression of TEOAEs was kept at 60 dB peak sound pressure level (Hood et al., 1996; Veuillet et al., 1991). The recommended contralateral suppressor was used as the broadband (white) noise (Berlin et al., 1993; Velenovsky & Glattke, 2002). The intensity for suppressor (broadband noise) was kept at 65 dB sound pressure level.

Instructions before the Baseline Recording and Silence Period

Knobel and Sanchez (2008) observed 68.2% of the participants (normal hearing adults) perceived tinnitus when seated in a sound booth for 5 minutes during an auditory attention task. However, the percentage of participants perceiving tinnitus reduced to 45.5% when participants were assigned a visual task during the silent period. This study demonstrated that visual task interferes with auditory attention task and tinnitus

perception. Therefore, participants were instructed not to talk, read, write, or text. In addition, participants were instructed to report the auditory experience they had during the 10 minutes of the silent period, if any. Participants were also instructed to disregard the auditory stimulus presented during the OAE tests administered before and after the silent period. These instructions were important because the participants needed to report their experience after the post-silent recording of TEOAE tests.

Baseline Recording of TEOAE Total Amplitude with and without Suppression (Pre-silence Recording)

Each participant was seated in a comfortable chair inside the sound booth for all TEOAE measurements. The TEAOE equipment Otodynamics was calibrated for all the testing parameters (stimulus and acquisition) before data collection procedure. OAE probe calibration was completed before testing each participant. The real ear probe calibration was performed using the ILO probe-fit check paradigm before running each OAE measurement. The probe (probe 1), with a suitable probe tip, was inserted in the right ear canal to obtain a firm but comfortable seal. The second probe (probe 2) was inserted in the left ear canal to obtain a firm but comfortable seal. The broadband white noise was delivered to the left ear for contralateral TEOAE suppression. Care was taken to ensure that the positions of the probes would not be altered throughout the duration of testing and silence. The simultaneous TEOAE recording with and without suppression was obtained using the recommended test parameters mentioned in the previous section.

Total TEOAE suppression amplitude was measured by subtracting total TEOAE suppression response from the total TEOAE response. Hood et al. (1996) found the

suppression variability across the subjects ranged from 0.07 to 0.36 dB with mean of 0.21 dB that was based on the standard error of the mean for each of the click intensity (50, 55, 60, 65, and 70 dB) and white noise (10 dB below the click intensity to 10 dB above the click intensity). Because stimulus and suppressor parameters in this study are similar to the parameters used in the Hood et al. (1996) study, the upper limit of the range (0.36 dB) was considered appropriate to test the suppression effect.

Silence Session

Once the baseline TEOAE and suppression of TEOAE measurements had been recorded, each participant remained sitting in the sound booth for a period of 10 minutes with the TEOAE equipment remaining in place. Participants were sitting quietly in a silence/sensory deprivation condition for the duration of 10 minutes.

Repeat TEOAE and Contralateral Suppression (Post-silence Recording)

TEOAE and contralateral suppression of TEOAEs were measured again to determine if there was any change from the baseline. Care was taken to ensure that the positions of the probes would not be altered throughout the duration of testing and silence. Any difference in the amount of suppression was attributed to the effect of silence/sensory deprivation.

Filling Out Questionnaire

Participants were unhooked from probes and allowed leave the sound booth. Participants were given a paper survey with three questions to indicate the kind of tinnitus perception (such as tone, buzz, cricket-like, ocean waves, roaring, etc.) that they may have experienced during the silence period. Participants completed a short written

survey to describe any tinnitus perceptions they might have noticed. (See Appendix C for this survey). The word “Tinnitus” was intentionally avoided in the tester’s instructions to prevent any apprehension about the auditory perception if any. This procedure was administered to let the auditory system recover from the changes that silence might induce.

Data Analysis

Descriptive and inferential quantitative statistical tests were used to analyze the data. Data was entered SPSS software (Version 20) spreadsheet. Descriptive statistics data was obtained from the case history form and tinnitus survey form on subject demographics, tinnitus sound heard, race and ear differences. It should be noted here that, whereas subjects did vary in race, the purpose of this preliminary study was to examine the effect of silence on TEOAE. Thus, the race was not used as a coding factor in ANOVA calculations.

De-identifier codes were used in the SPSS spreadsheet for data. The key for the de-identifier code was kept on a paper file in a locked cabinet at the desk of the investigator in CSD 327A. The SPSS spreadsheet that contains the data was located on the investigator’s office computer protected with a secure password. The investigator with secure login ID and password accessed the data. The raw data was stored in the laptop attached to the instrument Otodynamic echoport ILOV6 292-I in CSD 327-A. The test software was password protected. Only the investigator had access to login ID and password.

Research Hypotheses: Definition of Statistical Support

Hypothesis 1: The total transient otoacoustic emission amplitude values will be statistically significantly decreased after a period of 10 minutes of silence in test ear (right ear).

Definition of statistical support for hypothesis 1: Repeated measures analysis of variance (ANOVA) was administered for the repeated measure TEOAE amplitude before and after 10 minutes of silence.

Hypothesis 2: The transient otoacoustic emission suppression amplitude will be significantly increased after a period of 10 minutes silence in test ear (right ear).

Definition of statistical support for hypothesis 2: Repeated measures analysis of variance (ANOVA) was administered for the repeated measure TEOAE suppression amplitude before and after 10 minutes of silence.

Hypothesis 3: Participants perceiving tinnitus after 10 minutes of silence will have a greater amount of TEOAE suppression in post-silent measurement than the participants without the perception of tinnitus.

Definition of statistical support for hypothesis 3: Hood et al. (1996) found the suppression variability across the subjects ranged from 0.07 to 0.36 dB with mean of 0.21 dB that was based on the standard error of the mean for each of the click intensity (50, 55, 60, 65 and 70 dB) and white noise (10 dB below the click intensity to 10 dB above the click intensity). The upper limit of the range (0.36) was considered appropriate to test the suppression effect. One-way ANOVA was performed to assess the difference in post silence total TEOAE suppression amplitude between participants perceiving tinnitus and

non-perceiving tinnitus. Repeated measure Analysis of Variance (ANOVA) was performed to assess the overall suppression effect (Total suppression) before and after silence period between the participants perceiving tinnitus post-silence and non-perceiving participants.

CHAPTER IV

RESULTS

Tinnitus Perception

Descriptive statistics for the tinnitus perception, tinnitus localization, and types of tinnitus perception are shown in Table 1. The Tinnitus perception questionnaire was administered immediately to each subject after the completion of silence experiment. It can be seen that 41.4% (24 out of 58) of the total participants reported the perception of tinnitus during/after exposure to 10 minutes of silence. 58.6% (34 out of 58) did not report perceiving tinnitus during/after 10 minutes of silence. Majority of the participants (*n*=14/24, 58.3%) reported their tinnitus perception to be located in both ears. Five participants (20.8%) and three (12.5%) participants reported hearing their tinnitus in the head and right ear, respectively. The remaining two (8.3%) participants reported their tinnitus in the left ear. Considering the silence period of 10 minutes was introduced to both ears and the subjects had normal hearing in both ears, it was expected that the majority of tinnitus perception would be reported both ears.

Overall, “Ringing” was the most common type of tinnitus sound perception in the majority of participants who perceive tinnitus followed by “Cricket” and “Buzzing” sound. “Pulsating” or “Clear tone” sounds were less frequent followed by “Hissing,” “Ocean Roar,” and “Transformer.” “Only one participant reported hearing the “Ocean Roar” or “Transformer” sounds.

Table 1

Descriptive Statistics for Tinnitus Perception Questionnaire: Tinnitus Perception, Location, and Type

		n	Percent
Tinnitus Perception (*N*=58)	Yes	24	41.4%
	No	34	58.6%
Tinnitus Location (*N*=24)	Right ear	3	12.5%
	Left ear	2	8.3%
	Both ears	14	58.3%
	In the head	5	20.8%
Tinnitus Type (*N*=24)	Ringing	9	37.5%
	Cricket	5	20.8%
	Buzzing	3	12.5%
	Hissing	1	4.1%
	Pulsating	2	8.3%
	Clear Tone	2	8.3%
	Ocean Roar	1	4.1%
	Transformer	1	4.1%

Table 2 shows the demographic statistics of age, gender, and tinnitus perception according to the ethnicity. Age range of the participants was 18-35 years with the mean age 26.96 years. All 58 participants recruited in this study were male. Out of 40 Asian participants, 14 (35%) perceived tinnitus during or after 10 minutes of silence. Tinnitus perception was highest in Caucasian subjects and lowest in African American subjects. Out of 14 Caucasian participants, nine (64%) perceived tinnitus during or after 10

minutes of silence. Out of four African American participants, only one (25%) perceived tinnitus during or after 10 minutes of silence.

Table 2

Demographic Table: Age, Gender, and Tinnitus Perception and Ethnicity Descriptive Statistics

		Ethnicity				Age Range	Mean Age	Gender
		Asian	Caucasian	African American	Total (%)	18-35 Years	26.96	Male
Tinnitus	Yes	14 (35%)	9 (64.28%)	1 (25%)	24 (41.37%)	19–33	26.3	24
	No	26 (65%)	5 (35.72%)	3 (75%)	34 (58.62%)	19–34	26.6	34
Total		40	14	4	58	58		58

Silence on Transient OAEs

The Effect of Silence on Recording Transient OAE Amplitude

***Hypothesis 1*:** The total transient otoacoustic emission amplitude values will be statistically significantly decreased after a period of 10 minutes of silence in test ear (right ear).

Table 3 shows TEOAE and TEOAE suppression data analysis for pre and post 10 minutes silence period. Repeated measures ANOVA was conducted to compare the effect of 10 minutes of silence on total mean TEOAE and total TEOAE suppression amplitudes from pre-silence and post-silence conditions. All participants met "total TEOAE suppression 0.36 dB or more" criterion.

Statistical analysis revealed there was no statistically significant (Wilks' Lambda= .984, F (1, 57) = .948, p = .334) difference observed between pre- and post-10-

minutes silence total TEOAE amplitude in the right ear. See Figure 9 in Appendix D for the TEOAE waveform before and after 10 minutes of silence. (Note: The waveforms in Appendix D are from one of the participants in this study.) There was no effect of 10 minutes of silence on total TEOAE amplitude. This result indicates that the difference in means of pre- and post-10 minutes of silence TEOAE amplitudes are clinically non-significant. Therefore, exposing a subject to 10 minutes of silence period did not affect the subject's total Transient Otoacoustic Emission (TEOAE) amplitude.

The Effect of Silence on the Recording of the Suppression Amplitude of Transient OAEs

Hypothesis 2: The transient otoacoustic emission suppression amplitude will be significantly increased after a period of 10 minutes silence in test ear (right ear).

Table 3 also shows total TEOAE suppression data analysis before and after 10 minutes of silence. See Figure 10 in Appendix D for the TEOAE suppression waveform before and after 10 minutes of silence. Repeated measure ANOVA was conducted to compare the effect of silence on total TEOAE suppression amplitude. There was no significant effect of 10 minutes of silence on total TEOAE suppression amplitude (Wilks's Lambda= .995, F (1,57) = .304, p = .584). It was observed that the total TEOAE suppression amplitudes were not significantly different between pre and post 10 minutes silent measurement. Therefore, like TEOAE amplitude before silence, total TEOAE suppression amplitude was not affected by 10 minutes of the silence period.

Table 3

Descriptive Statistics and Summary of Repeated Measure ANOVA of TEOAE and TEOAE Suppression Amplitudes: Pre- and Post- 10 Minutes of Silence

	10-min Silence	*N*	*M*	*SD*	*df*	*F*	Sig.
Total TEOAE Amplitude	Pre-Silence	58	11.4897	4.9021	1	.948	.334
	Post-Silence	58	11.5828	5.0069			
Total TEOAE Suppression Amplitude	Pre-Silence	58	.9259	.7470	1	.304	.584
	Post-Silence	58	.8931	.7525			

The Effect of Tinnitus Perception Due to Silence and the Amplitude of OAE Suppression

Hypothesis 3: Participants perceiving tinnitus after 10 minutes of silence will have a greater amount of TEOAE suppression in post-silent measurement than the participants without the perception of tinnitus.

Table 4 shows the results of the one-way ANOVA measurement with 1 dependent variable (Post-Silence Total TEOAE Suppression) and two groups of factor tinnitus (Participants perceiving tinnitus during/after 10 minutes of silence and Participants who did not perceive tinnitus). The results of the one-way ANOVA showed that there is no statistically significant (F (1,56) = .220, ns) difference in post silence total TEOAE suppression amplitude between two groups. There is no significant difference in post silence total TEOAE suppression due to tinnitus perception. This result indicates that the perception of tinnitus after a brief period of silence did not results in a significant change in the total suppression of TEOAE amplitude.

Table 4

Descriptive Statistics and One Way ANOVA for Post Silence Total TEOAE Suppression Amplitude between Tinnitus Perceiving Participants and Participants not Perceiving Tinnitus

					Post-Silent TEOAE Suppression		
	Perception	*N*	*M*	*SD*	*df*	*F*	Sig.
Tinnitus	Yes	24	.8375	.83030	1	.220	.641
	No	34	.9324	.70269			

Table 5 shows the summary of the Repeated Measure ANOVA. The Repeated Measure ANOVA with two within-subject factors (Pre-silence total TEOAE suppression and Post Silence total TEOAE suppression) and one between subjects factor (Tinnitus perception) were applied to evaluate group difference. The main effect of tinnitus perception (F (1, 56) = 0.486, p = 0.489) was not to be statistically significant in TEOAEs. The data further indicates that there was no statistically significant (F (1,56) = 0.405, p = 0.527) difference between pre-post 10 minutes silence total TEOAE suppression (PrePostSup) between participants who perceived tinnitus and participants who did not perceive tinnitus during/after 10 minutes of silence.

Table 5

Summary of Repeated Measure ANOVA: Main Effect of Tinnitus, Pre- and Post-Silence—Tinnitus Interaction on Total TEOAE Suppression Amplitude

Source	Mean Square	*df*	*F*	Sig.
Intercept	90.758	1	88.017	.000
Tinnitus	.501	1	.486	.489
Tinnitus*PrePostSup	.042	1	.405	.527
Error	57.743	56		

CHAPTER V

DISCUSSION

The purpose of this study was to investigate the effect of silence on TEOAE and TEOAE suppression, wih the emergence of temporary tinnitus perception as an analysis factor. Additionally, this study reports on the demographics on temporary tinnitus perception after a brief period of silence.

Tinnitus Perception and Silence Demographics

One goal of the current study was to expand upon the findings of Tucker et al. (2005) to document the emergence of temporary tinnitus in normal hearing young adults after a short period of silence. To date, few studies have explored the emergence of temporary tinnitus perception after a brief period of silence in normal hearing adults. Tucker et al. (2005) reported a total mean of 64% overall tinnitus perception in young adults with normal hearing after a period of silence. Additionally, they reported finding a significant race difference in tinnitus perception, with a high percentage of Caucasians (78%) perceived tinnitus after silence than African American (38%). The landmark article in tinnitus and silence is from Heller and Bergman's (1953) study, who found 93.75% normal hearing adults experienced tinnitus perception after a period of silence.

The current study found that 41.4% of the total participants perceived some type of tinnitus during/after 10 minutes of silence. This overall finding was lower than that of Heller and Bergman (1953) and for the Caucasians reported in Tucker et al. (2005). The

findings of the current study may differ from the work of Heller and Bergman due to the age range of the self-reported normal hearing participants were 10-68 years in their study and that self-reported hearing might have neglected the actual hearing loss at higher frequencies due to old age. That untested hearing loss might have caused the higher percentage of tinnitus perception participants.

The finding of the current study was also lower than that reported by Tucker et al. (2005) and possibly can to be attributed to the difference in race/ethnicity of the participants. The current study had 69% of Asian participants, and the overall low result of 41.4% of subjects perceiving tinnitus may suggest that Asian participants, like African American participants reported in Tucker et al. (2005), are less likely to perceive tinnitus in/after the silence.

As reported in Tucker et al.'s (2005) study, a high percentage of Caucasians perceived tinnitus. In present study, 64.28% of Caucasians perceived tinnitus after/during 10 minutes of silence as compared to 35% Asian and 25% African American. However, only 24.13% of participants were Caucasians in the present study. Considering that the Caucasians are more likely to report tinnitus in silence, it would have been beneficial for the present study to include a high percentage of Caucasians instead of Asian.

The Role of the Medial Olivocochlear Efferent Pathway and Tinnitus Perception

The primary goal of the current study was to identify the possible role of the medial olivocochlear efferent neural pathway in the perception of tinnitus in the presence of silence. The function of the medial olivocochlear efferent neural pathway was assessed

using the transient otoacoustic emission suppression tests. Three hypotheses were proposed:

1. The total transient otoacoustic emission amplitude values will be statistically significantly decreased after a period of 10 minutes of silence in test ear (right ear).
2. The transient otoacoustic emission suppression amplitude will be significantly increased after a period of 10 minutes silence in test ear (right ear).
3. Participants perceiving tinnitus after 10 minutes of silence will have a greater amount of TEOAE suppression in post-silent measurement than the participants without the perception of tinnitus.

The Effect of Silence on the TEOAE Amplitude

TOAE waveform amplitude was selected as a means of assessing the medial olivocochlear neural pathway. Changes in this lower brainstem neural function after exposure to silence would be reflected/recorded in the amplitudes of the TEOAE and the TEOAE with suppression (introduction of masking noise to the stimulus). Results of the present study found that the total TEOAE amplitudes (with and without suppression) were not statistically significantly different before and after 10 minutes of silence. To our knowledge, this study is the first research study that aims at identifying the statistical difference in TEOAE and TEOAE suppression amplitude in single sitting session and to observe the effect of 10 minutes of silence on TEOAE and TEOAE suppression. This preliminary finding would suggest that the exposure to a brief period of silence does not alter the neural functioning of the lower central auditory neural pathway. This finding

supports (Eggermont, 2012; Eggermont & Komiya, 2000; Eggermont & Roberts, 2004) which indicate that the generation of tinnitus is more likely thalamic or higher cortical in origin.

There could be alternative explanations to the findings of the present study:

- Ten minutes of silence (sensory deprivation) may not have been sufficient to induce hyperactivity in the cochlear nucleus or medial olivocochlear efferent neural pathway enough to inflict significant TEOAE suppression. However, other studies (Bo et al., 2008; Knobel & Sanchez, 2008) report the emergence of temporary tinnitus perception after just five/four minutes of silence.
- Ten minutes of silence (sensory deprivation) may not be sufficient to cause the significant alteration in the cochlear biochemical processes to change the TEOAE amplitude.
- Post silent changes in the cochlea or hyperactivity in the cochlear nucleus and/or efferent auditory pathways were quickly recovered after the stimulus presentation (stimulus presentation during post silence TEOAE and TEOAE suppression recording) to eliminate detection of any changes in the TEOAE or TEOAE suppression.

Additional research is needed in the effects of brief periods of silence on TOAE amplitude to further our understanding of the contribution of the lower CANS in the perception of tinnitus.

Tinnitus and Silence

The Effect of Tinnitus Perception on TEOAE Amplitude

The results of the current study found no statistically significant difference in post-silent total TEOAE suppression between tinnitus perceiving participants and non-perceiving participants. The data in Table 5 further indicates that there was no statistically significant difference between pre-post 10 minutes silence total TEOAE suppression (PrePostSup) between participants who perceived tinnitus and participants who did not perceive tinnitus. There is no interaction effect between tinnitus and pre-post silent TEOAE suppression.

Tinnitus is a central, rather than a peripheral auditory phenomenon. Some form of cochlear damage initiates the neuroplasticity changes in the central auditory system that underlies the pathophysiology of tinnitus (Eggermont & Roberts, 2004; Kaltenbach, 2011; Møller, 2007; Roberts et al., 2010). The cochlear damage could be because of noise trauma; ototoxicity or age-related hearing loss. Noreña and Farley (2013) proposed that residual peripheral spontaneous activity and central auditory gain due to peripheral damage collectively contribute to the tinnitus perception. Changes in the spontaneous firing rate of many different structures within the central auditory system have been shown after cochlear damage (Kaltenbach, 2011; Mulders & Robertson, 2009; Volger, Robertson, & Mulder, 2011). In the present study, the participants did not have any peripheral cochlear damage as assessed by audiometric test and otoacoustic emission tests. Therefore, 10 minutes of silence might not have produced the pathophysiological changes in the central auditory system, especially hyperactivity in the dorsal cochlear

nucleus. This also suggests that the pathophysiology of tinnitus perception in patients with cochlear damage (hearing loss of some degree) might be different than silence induced tinnitus in normal hearing individuals.

Noise trauma, ototoxic medication, or ages related hearing loss are related to the tinnitus in humans. Therefore, possibly, multiple mechanisms that lead to some form of central neuroplastic changes play a role in tinnitus perception. Similarly, silence induced tinnitus might have the mechanism that might not involve an alteration in the medial olivocochlear efferent pathway, although further investigation is needed.

Several studies have found dysfunction of the medial olivocochlear efferent pathway in humans with tinnitus compared to normal hearing sensitivity (Fernandes & Santos, 2009; Granjeiro et al., 2008; Paglialonga, Fiocchi, Del Bo, Ravazzani, & Tognola, 2011; Riga et al., 2007). In these studies, although subjects had normal hearing sensitivity, they already had the tinnitus. A trigger of tinnitus in these subjects might be cochlear dead regions that go undetected in audiometry and even in otoacoustic emissions if such dead regions are outside the frequency range of testing. Similarly, the hearing loss also might go undetected in the frequency range outside the testing frequencies. Such cochlear dead regions and hearing loss can initiate neuroplastic changes in the central auditory system that leads to tinnitus perception.

In the present study, all participants had a normal hearing and they did not have tinnitus. Therefore, silence might not have induced medial olivocochlear dysfunction in both tinnitus perceiving participants and non-perceiving participants. In participants who did not perceive tinnitus, silence might not have induced the neuroplastic changes in the

central auditory system. In participants who did perceive tinnitus, silence might have induced temporary neural changes in the central auditory system, but not in the medial olivocochlear efferent or dorsal cochlear nucleus, that lead to tinnitus perception. As discussed in the previous section, silence induced tinnitus might have a different mechanism than tinnitus associated with hearing loss.

Corticofugal auditory system in humans. The functional corticofugal efferent system runs from cortex to the cochlea (Perrot et al., 2005). The findings of this study suggest the functional connection between the auditory cortex and contralateral outer hair cell in humans. The medial olivocochlear efferent pathway acts as the final connection in corticofugal efferent system between superior olivary complex and contralateral outer hair cells (Perrot et al., 2005). The electrical stimulation of the auditory areas in this system resulted in the significant reduction of the contralateral evoked otoacoustic emission amplitude. This corticofugal efferent system influences lower auditory brainstem structures such as medial olivocochlear neuronal pathway and cochlear nucleus.

Top-down influence of the attention plays a significant role in alteration of cerebral cortical area function (Gilbert & Sigman, 2007). Auditory cortex and other cortical areas are influenced by the auditory attention (Justerboff, 1999). Auditory attention can influence the lower auditory structures such as medial olivocochlear bundle and cochlear nucleus via the corticofugal efferent pathway. In this study, participants might have sought the sound perception during the period of silence (auditory attention). Such auditory attention might have suppressed the hyperactivity in the medial

olivocochlear efferent pathway or cochlear nucleus through corticofugal efferent feedback. Therefore, corticofugal top-down efferent feedback might have inhibited any change in the TEOAE suppression amplitude after 10 minutes of silence.

TEOAE suppression and tinnitus. As mentioned earlier in the literature review, abnormally small or no suppression was observed in the contralateral suppression of TEOAE test in tinnitus patients with a normal hearing sensitivity (Chéry-Croze et al., 1993; Veuillet et al., 1991). However, according to the theoretical model of this study, it was hypothesized that there would be more suppression in participants perceiving tinnitus compared to participants not perceiving tinnitus. This discrepancy could be explained in the context of the lack of peripheral inhibition theory. The subjects in the above-mentioned studies had a normal hearing. Therefore, it is not expected in these patients to have hyperactivity in the cochlear nucleus and subsequent hyperactivation in the medial olivocochlear efferent pathway. Therefore, it is also not expected in these tinnitus patients to have more suppression. On the contrary, these patients had abnormal small or no suppression. Such findings could be the effect of corticofugal efferent auditory system feedback (Explained in the previous section). In these tinnitus patients, the constant awareness and attention to the tinnitus and associated psychological factors might have influenced the auditory cortex and in-turn sent inhibitory feedback to the medial olivocochlear efferent pathway through the corticofugal system. Such negative feedback inhibited the medial olivocochlear efferent pathway and consequently abnormally small or no suppression was observed in the contralateral suppression of TEOAE test.

In the present study, the participants perceiving tinnitus also may have sought the sound perception during silence and in such participants abnormally small or no suppression was expected because of negative corticofugal auditory feedback. However, in the present study, there was no significant difference in suppression between tinnitus perceiving and non-perceiving tinnitus. The lack of peripheral inhibition due to silence may have initiated the hyperactivity in the cochlear nucleus (according to the theoretical model of this study). Such hyperactivity in the cochlear nucleus may have canceled out the negative feedback effect from the corticofugal pathway. Thus, there was no effect of silence on TEOAE suppression amplitude.

Although corticofugal feedback has the influence on the theoretical model of this study and seems to be the missing piece, the theoretical model still holds its notion in the context of this study. The non-significant results in this study can be attributed to the inadequacy of TEOAE tests in measurement of brainstem structures. The TEOAE suppression test is an indirect measure of cochlear nucleus hyperactivity. In this study, the inferences about the cochlear nucleus hyperactivity were based on changes in the cochlear phenomenon (TEOAE changes). In addition, TEOAE suppression test is noninvasive procedure, which cannot directly measure the cochlear nucleus hyperactivity or MOC hyperactivity.

Abnormal suppression of medial olivocochlear pathway was also observed using DPOAE suppression in normal hearing tinnitus patients (Riga et al., 2007). The DPOAE suppression results are to be observed with caution because the phase relationship between two frequencies in the DPOAE stimulus greatly influences the results of the

DPOAE test. This phenomenon and shortcomings of the DPOAE tests in relation to the assessment of medial olivocochlear function is explained in the "Tinnitus and suppression of otoacoustic emission" section of the literature review. Abnormally small suppression in this study may be attributed to the phase relationship phenomenon.

Limitations of the Study

The otoacoustic emission tests used in this study are non-invasive tests. Although contralateral suppression of otoacoustic emission provides information about the function of the medial olivocochlear efferent pathway, these tests might not have assessed the altered function of the efferent after a period of silence. The post-silent changes in the cochlea or hyperactivity in the cochlear nucleus and/or efferent auditory pathways was recovered soon enough after the stimulus presentation (stimulus presentation during post silence TEOAE and TEOAE suppression recording) to eliminate any changes in the TEOAE or TEOAE suppression.

The continuous contralateral suppressor noise method was used to assess the TEOAE and TEOAE suppression. It is possible that residual inhibition (carryover of suppression following stimulation) in the masker "ON" condition might have impacted the TEOAE response in the masker "OFF" condition. Consequently, the difference between TEOAE amplitude and TEOAE amplitude after suppression could have reduced. This could have affected the total TEOAE suppression amplitude. It is also possible that after a period of silence, noise in the masker "ON" condition could have canceled out any changes in the auditory structures by the silence.

It seems like TEOAE tests may not be suitable for the assessment of MOC function related to hyperactivity in the cochlear nucleus. If post silence test stimulus presentation cancels out the auditory changes before they get recorded then indirect measurement of MOC function could be done. Such indirect measurement of MOC function related to hyperactivity in the cochlear nucleus is explained in the context of musician-non-musicians study in the following future direction section.

Future Directions

Whereas tinnitus is thought to be central auditory processing phenomenon, results of this study indicate that the medial olivocochlear components of the central auditory nervous system appear not to be a strong contributing factor in the perception of temporary tinnitus and TEOAEs are not affected by the period of silence. Therefore, assessment of auditory structures like cochlear nucleus seems a promising area of research. Perrot and Collet (2014) reported stronger medial olivocochlear function in musician than non-musician. It would be useful information to observe the auditory brainstem response wave III amplitude in the musician. Auditory brainstem response wave III originates from cochlear nucleus. Therefore, if this wave III amplitude in musician has significantly larger amplitude than non-musician, that might give indirect connection to hyperactivity in the cochlear nucleus and consequential stronger medial olivocochlear response in the musician. This connection would be extended to the tinnitus perception by administering silence experiment in the musician with normal hearing and non-musician with normal hearing.

Tinnitus retraining therapy shows remarkable improvement in above 80% of the patients with any type of tinnitus (Jastreboff, 2011). The function of the medial olivocochlear efferent could be assessed before and after the tinnitus retraining therapy. It could provide important information about the possible role of medial olivocochlear efferent in tinnitus perception. In addition, such study could explore if alterations in the medial olivocochlear function are associated with any particular type of tinnitus.

Tucker et al. (2005) observed the effect of 20 minutes of silence on 120 normal-hearing young adults (60 male and 60 females with 40 Caucasians and 20 African Americans in each gender group). A significant difference was observed between races with tinnitus perception more common in Caucasian listeners (78%) than African American listeners (38%). Assessment of medial olivocochlear efferent using suppression of otoacoustic emission could be extended to a different race to observe the connection between efferent pathway and tinnitus in a different race. A future study could recruit more Caucasian and African American subjects to this database and then the data could be run with race as the main effects variable, to see if the finding of Tucker et al. (2005) is supported in showing subjects with darker skin tones are less likely to perceive tinnitus after a period of brief silence.

Conclusions

No statistically significant difference was found in total TEOAE and TEOAE suppression amplitude after 10 minutes of silence. Tinnitus perceiving participants did not show a statistically significant difference in total TEOAE suppression amplitudes after 10 minutes of silence than tinnitus non-perceiving participants. No interaction effect

was found between pre-post silence suppression and tinnitus perception. The TEOAE generation is a peripheral phenomenon. Because tinnitus perception did not significantly change total TEOAE amplitude, the results may indicate higher central auditory structures as a source of tinnitus generation. Therefore, the results of the study support the notion that tinnitus is the central auditory processing phenomenon. The study may have failed to detect the changes in the medial olivocochlear efferent pathway because TEOAE tests might not be sensitive enough to detect the post-silence changes in the pathway or top-down influence of the corticofugal pathway on lower auditory brainstem structures. This does not mean that medial olivocochlear efferents do not participate in tinnitus perception. Results of the present study also seem to indicate that race may place a function in the perception of silence induced temporary tinnitus. Further investigation is needed to evaluate the functional contribution of the medial olivocochlear efferent pathway in tinnitus perception.

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APPENDIX A

LIST OF ABBREVIATIONS

Abbreviation	Full Name
AI	Primary Auditory Cortex
AMPA	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid
ANF	Auditory Nerve Fibers
AVCN	Anterior Ventral Cochlear Nucleus
CANS	Central Auditory Nervous System
CF	Characteristic Frequency
COX	Cyclooxygenase
CN	Cochlear Nucleus
DCN	Dorsal Cochlear Nucleus
DPOAE	Distortion Product Otoacoustic Emissions
EAE	Enhanced Acoustic Environment
FC	Fusiform Cell
GABA	Gamma-Aminobutyric Acid
IC	Inferior Colliculus
ICc	Central Nucleus of Inferior Colliculus
IHC	Inner Hair Cell
LOC	Lateral Olivocochlear Neurons
MOC	Medial Olivocochlear Neurons
NMDA	*N*-methyl-D-aspartate
OAE	Otoacoustic Emission
OCB	Olivocochlear Bundle
OHC	Outer Hair Cell
PVCN	Posterior Ventral Cochlear Nucleus

Abbreviation	Full Name
RNS	Reactive Nitrogen Species
ROS	Reactive Oxygen Species
SFR	Spontaneous Firing Rate
SOAE	Spontaneous Otoacoustic Emission
SOC	Superior Olivary Complex
SPL	Sound Pressure Level
TEOAE	Transient Evoked Otoacoustic Emission
TMJ	Temporomandibular Joint
VCN	Ventral Cochlear Nucleus

APPENDIX B

CASE HISTORY QUESTIONNAIRE

Case History Questionnaire

Subject Number: _____ Date: _____ Age: _____

Questions about Hearing Status:	Yes	No
1. Do you have a ringing in the ears? (Tinnitus)		
2. Do you have a hearing loss?		
3. Do you have a history of ear infections?		
4. Do you currently have any discharge coming from your ears?		
5. Do you currently have tubes in your eardrum?		
6. Do you have a feeling of spinning, whirling, or dizziness?		
7. Do you have a feeling of fullness or pressure in your ears?		
8. Have you ever had surgery on your ears?		
9. Have you been exposed to intense noise exposure (e.g., industrial noise) for long time?		
Questions about Neurological Status:		
10. Do you have a history of seizures?		
11. Do you have a history of brain injury or head trauma?		
12. Do you have a history of a brain tumor or the ear?		
13. Do you have a history of any neurological disorder?		

14. Do you have any other medical history that might affect your hearing?		
If yes, please specify		

Audiogram: ____ Normal ____Abnormal

Otoscopy: Right ear: ____Normal _____Abnormal

Left ear: ____Normal _____Abnormal

Tympanogram: Right ear: ____ Normal _____ Abnormal

Left ear: ____ Normal _____ Abnormal

Admission to Study: _____Yes ____No

Medical Referral: _____Yes ____No

APPENDIX C

SOUND PERCEPTION QUESTIONNAIRE

Sound Perception Questionnaire: Test ear: _____
Subject Number: _____ Date: _____ Age: _____
1. Did you hear any sounds after 10 minutes of silence?

YES	NO

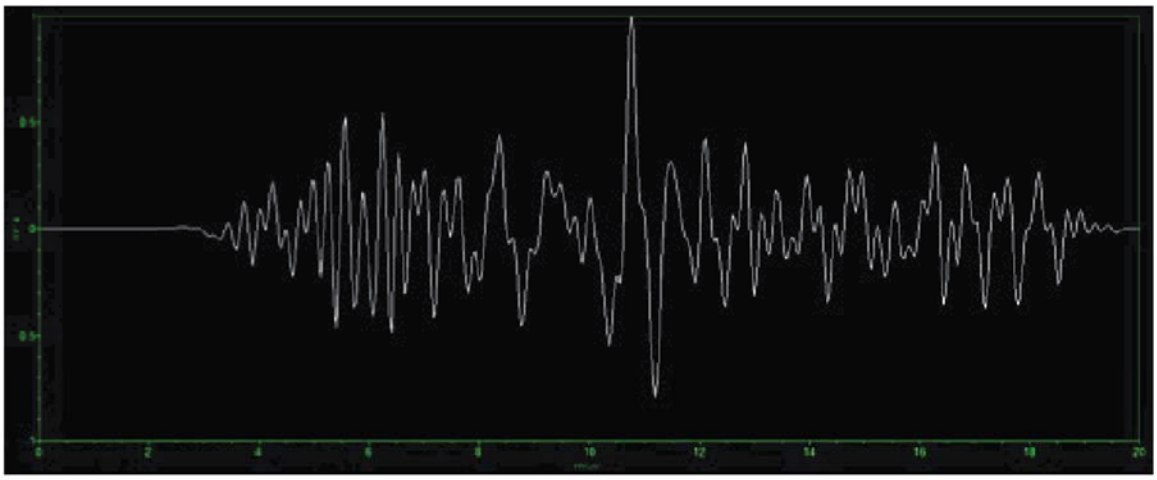
2. If YES, in which ear did you perceive the sound?
Right: ____ Left: _____ both ears: _____ or, in the head: _____

3. What type of sound(s) you perceived? Check the box next to the type of sound close to the sound you perceived after 10 minutes of silence. Check all that apply.

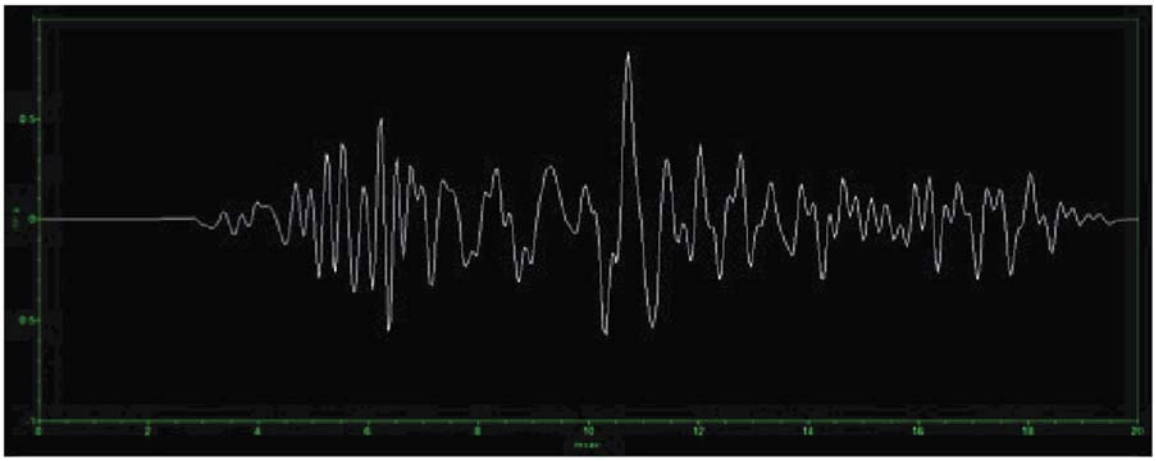
Type of Sound	Check if you heard this sound.
Ringing	
Whistle	
Crickets	
Buzzing	
Hissing	
Hum	
Pulsating	
Clear tone	
Ocean Roar	
Transformer	
Other: (please describe)	

APPENDIX D

TEOAE WAVEFORMS

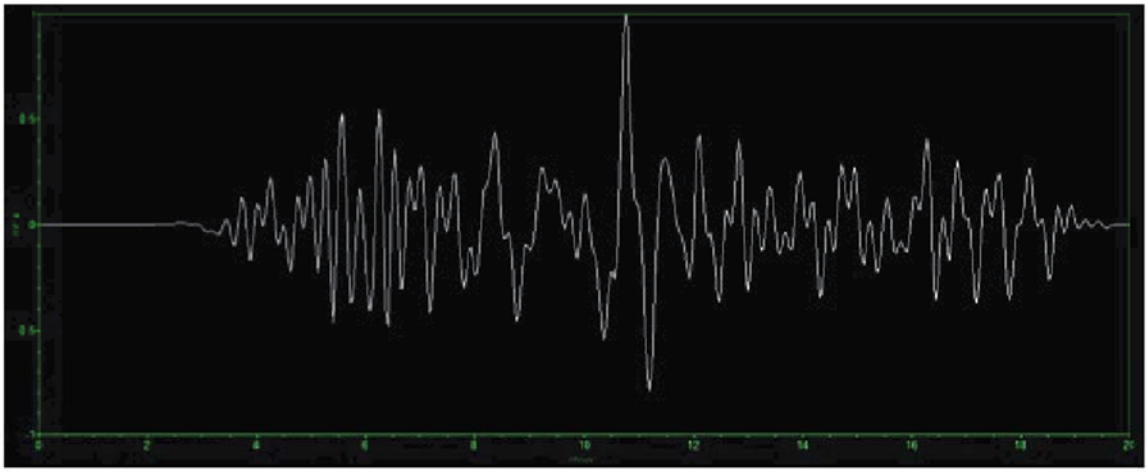


a) TEOAE waveform Before Suppression

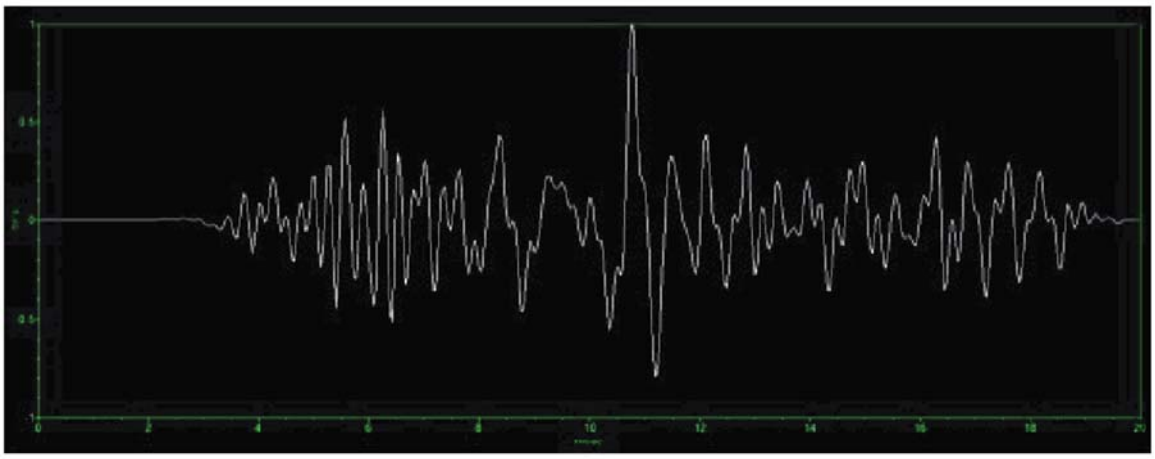


b) TEOAE waveform after suppression

Figure 8. TEOAE Suppression Waveform a) before and b) after 10 Minutes of Silence, Measured from One of the Participants in This Study. The X-axis Represents the Time-averaged Waveforms Sampled for a 20-ms Period Following the Onset of the Transient Stimulus. Y-Axis Represents Amplitude of the Waveform in mPa. a) TEOAE Waveform before Suppression; b) TEOAE Suppression Waveform after Suppression. We Can See the Reduced Amplitude in TEOAE Waveform after Suppression.

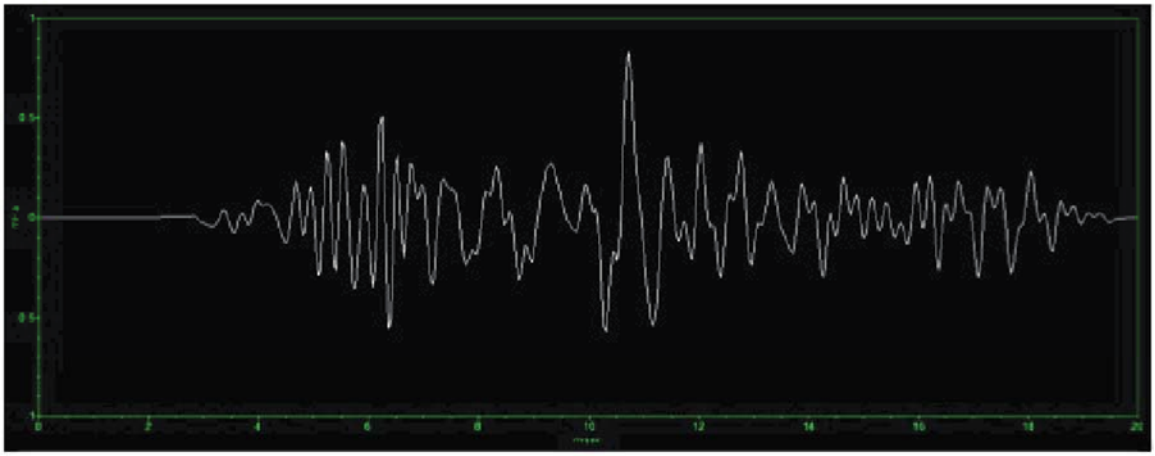


a) Pre-silence TEOAE waveform

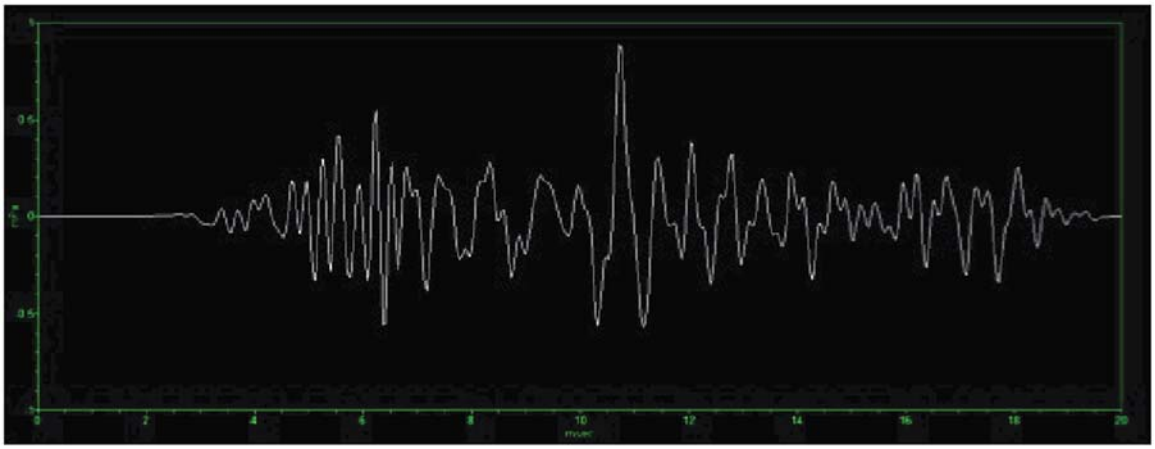


b) Post-silence TEOAE waveform

Figure 9. TEOAE Suppression Waveform a) before and b) after 10 Minutes of Silence, Measured from One of the Participants in This Study. As We Can See, There is No Significant Change in the Waveforms before and after 10 Minutes of Silence. TEOAE Amplitude is Almost the Same after 10 Minutes of Silence.



a) Pre-silence TEOAE suppression waveform



b) Post-silence TEOAE suppression waveform

Figure 10. TEOAE Suppression Waveform a) before and b) after 10 Minutes of Silence, Measured from One of the Participants in This Study. As We Can See, There is No Significant Change in the Waveforms before and after 10 Minutes of Silence. TEOAE Suppression Amplitude is Almost the Same after 10 Minutes of Silence.

APPENDIX E

INFORMED CONSENT

UNIVERSITY OF NORTH CAROLINA AT GREENSBORO

CONSENT TO ACT AS A HUMAN PARTICIPANT

Dissertation topic Title: " Role of Medial Olivocochlear Neural Efferent Pathway in Perception of Tinnitus in Presence of Silence "

Principal Investigator and Faculty Advisor: Amitkumar Tayade & Dr. Denise Tucker

Participant's Name: _____

What are some general things you should know about research studies?
Research studies are designed to obtain new knowledge. This new information obtained in these studies may help society in the future. There may not be any direct benefit to you for being in the research study. There also may be risks to being in research studies. If you choose not to be in the study or leave the study before it is done, it will not affect your relationship with the researcher or the University of North Carolina at Greensboro. Details about this study are discussed in this consent form. It is important that you understand this information so that you can make an informed choice about being in this research study.

You are being asked to take part in a research study. Your participation in the study is voluntary. You may choose not to join, or you may withdraw your consent to be in the study, for any reason, without penalty.

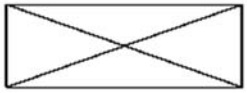
You will be given a copy of this consent form. If you have any questions about this study at any time, you should ask the researchers named in this consent form. Their contact information is below.

What is the study about?
The purpose of this study is to examine the short-term effects of a brief period of silence on human hearing in young adult males. We will examine the changes (if any) of small ear-echoes that we can record in the right ear canal after a period of ten minutes of silence. We will also examine if this effect can be reduced by delivering a medium shower-like masking sound (for brief period) in the left ear.

Why are you asking me?
Because you are adult male between the age range 18-35 years and have normal hearing thresholds.

What will you ask me to do if I agree to be in the study?

1. You will be asked to read and sign the consent form.
2. You will be asked to provide brief case history about your hearing and exposure to noise. You will also have a hearing test to see if your hearing is normal. If you have hearing thresholds above the normal range, you will be dismissed from the



study and a referral to a hearing professional will be made if necessary.

3. You will be seated in a sound booth and will have a small plastic probe inserted in your both ears. You will then hear some sounds to record the Otoacoustic emission, Transient Evoked Otoacoustic emission (TEOAE) and its contralateral suppression tests.
4. You will then sit (with minimal movements for 10 minutes of silence in sound booth.
5. You will then have another TEOAE and its suppression test.
6. Then you will be asked to fill out short survey re: any the altered auditory perception, if any, during the period of silence.
7. The entire testing session will take approximately 45 minutes.

Brief case history: You will be asked to provide information about your audiological history. The questions will be similar to the following"

a) Do you ever have any type of ear surgery?
b) Do you ever have ear discharge?
c) Do you ever experience earache?

The explanation of the tests are listed below

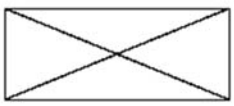
Pure tone Audiometry: This is a test to assess your hearing thresholds. In this test, you will wear headphones and hear sounds of different frequency tones. You will try to detect the softest sound you could hear. You will raise your hand/press the response button when you hear a tone. The threshold exceeding 25 dBHL at any test frequency will disqualify you as a participant in this study. If you will not qualify, all your data including consent form and case history will be destroyed.

Impedance Audiometry: This test assesses the middle ear function. This is objective test and the instrument carries all measurements automatically. Therefore, participant is expected to be relaxed and calm during the testing. The reflection of sound as a result of middle ear function will be measured by Impedance audiometer when a small ear probe will be inserted in the ear canal.

If the Impedance Audiometry suggests any middle ear dysfunction or central pathology, then you will not be qualified for this study. All your data including consent form and case history will be destroyed.

Transient Otoacoustic Emission Tests (TEOAE): You will be asked to sit on comfortable recline chair in the sound booth. A soft plastic probe tip will be inserted in the both ear canals. One probe can present the sound to your one ear and has a small microphone inside to record the ear echo. Sounds are delivered to the ear and the microphone in the ear canal records the echo response to that sound from the same ear. The other ear probe will deliver white noise (shower-like sound) at levels safe to the ears. This noise will assess the function of specific neural pathway that we are interested in.

Silence Measurement: After the TEOAE test, you will be asked sit in the same position with OAE probes in both ears for 10 minutes. You will be instructed to sit quietly and not



be allowed to read or write or text. After 10 minutes of silence, a second TEOAE will be done.

After the completion of the tests, the probe will be removed from your ear, and you will be asked to list any sounds you heard during the period of silence.

Is there any audio/video recording?
There will not be any audio or video recording

What are the risks to me?
The Institutional Review Board at the University of North Carolina at Greensboro has determined that participation in this study poses minimal risk to participants. In Contralateral suppression of OAE tests, 65 dBSPL white noise will be delivered to the ear canal, which is considered as safe by Occupational Safety and & Health Administration (OSHA). If you find it discomforting, the testing procedure will be terminated.

If you experience any discomfort in sitting inside the sound booth, the test can be performed with the door of the sound booth open instead of being closed.

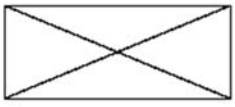
If you have questions, want more information or have suggestions, please contact Amitkumar Tayade and Dr. Denise Tucker who may be reached at (333) 681-0047 and (336) 256-2004, respectively. (Emails: agtayade@uncg.edu and datucker@uncg.edu).

If you have any concerns about your rights, how you are being treated, concerns or complaints about this project or benefits or risks associated with being in this study please contact the Office of Research Integrity at UNCG toll-free at (855)-251-2351.

Are there any benefits to society as a result of me taking part in this research?
Over 20 million Americans struggle with troublesome effects of tinnitus. Tinnitus is the ringing in the ear when there is no sound around. Such ringing in the ear has a negative impact on a patient's overall health and social well-being. Tinnitus can be a disabling condition. People with tinnitus regularly experience distress, depression, anxiety, sleep disturbances, frustration, poor concentration and in some cases pain. Currently, there are no scientifically validated cures available for most types of tinnitus. There is a gap between the brain structure involved in the tinnitus generation and treatment strategies for the tinnitus. The scientific knowledge from this study will provide the suitable tool for the assessment of certain brain structures that could contribute in perception of tinnitus. The assessment of such brain structures may open up new avenues leading to the better treatment options for patients suffering from tinnitus.

Are there any benefits to *me* for taking part in this research study?
Your hearing status and middle ear function will be tested free of cost and you will get a copy of the audiometry and immittance test results.

Will I get paid for being in the study? Will it cost me anything?
You will also get $10 amazon gift card after completion of all tests. This study will not cost you anything.



How will you keep my information confidential?
The selected participants for this study will be identified by number code. The number code is assigned to each participant at the time of testing. The consent form will have number and name of the participant. In the testing data sheet, names will not be associated with data. The number codes will be associated with the data.

The OAE test data will be stored on password-protected laptop in the laboratory. Only principal investigator and faculty advisor will have access to this data. The consent forms will be kept securely in a locker situated in principal investigator's office. Only principal investigator and faculty advisor will have access to the consent forms. All information obtained in this study is strictly confidential unless law requires disclosure.

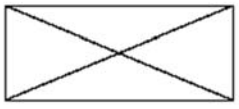
What if I want to leave the study?
You have the right to refuse to participate or to withdraw at any time, without penalty. If you do withdraw, it will not affect you in any way. If you choose to withdraw, you may request that any of your data, which has been collected, be destroyed unless it is in a de-identifiable state. The investigators also have the right to stop your participation at any time. This could be because you have had an unexpected reaction, or have failed to follow instructions, or because the entire study has been stopped.

What about new information/changes in the study?
If significant new information relating to the study becomes available which may relate to your willingness to continue to participate, this information will be provided to you.

Voluntary Consent by Participant:
By signing this consent form, I am agreeing that I read, or it has been read to me, and I fully understand the contents of this document and am openly willing consent to take part in this study. All of my questions concerning this study have been answered. By signing this form, I am agreeing that I am 18 years of age or older and am agreeing to participate in this study described above and will receive a copy of this consent forms.

Participant's Name (Print): _____

Signature: _____ Date: _____



APPENDIX F

RECRUITMENT FLYER

THE UNIVERSITY of NORTH CAROLINA
GREENSBORO

Department of Communication Sciences & Disorders

You are invited to participate in a doctoral study that explores the short-term effects of a brief period on silence on human hearing.

Who can participate:

- Male students with age between 18-35 years
- Subjects with no medical history of balance, neurological, and hearing disorders (including prolonged history of noise exposure resulting in a hearing loss)

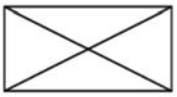
About the Study:

- Testing will take approximately 45 minutes.
- Participants with normal hearing thresholds will be included in the study.
- Participants are required to complete a brief case history about their hearing and to sit in the sound booth during hearing test procedures and during the 10 minutes of silence.
- We will also examine if this effect can be reduced by placing a medium shower-like masking sound in the left ear.
- Participants are required to fill up short survey re: the perception of sound (if any) during the period of ten minutes of silence in sound booth.

Every participant will receive a free hearing test and a $10 amazon gift card after the completion of testing.

For more information and to schedule an appointment, please contact Mr. Amitkumar G. Tayade. Phone (336)-681-0047 or at agtayade@uncg.edu

Location of study: 327-A, Ferguson building,



APPENDIX G

RECRUITMENT SCRIPT (IN-PERSON)

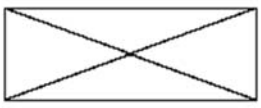
Recruitment Script (In-person)

Hello, My name is Amitkumar Tayade. I am a Doctoral student from Communication Sciences and Disorders department at University of North Carolina, Greensboro, and I would like to invite you to participate in a research study. I am conducting my study to observe *the short-term effects on hearing after a brief period of silence.* I will also examine if these effects can be reduced by delivering a medium shower-like masking sound (For brief period) in the left ear. I want to study this in young adults males with normal hearing. You may participate if your age is within 18-35 years and you don't have any medical history related to hearing or hearing loss. Please do not participate if you have hearing loss or have any medical history affecting your hearing.

Participation in this study includes providing brief medical history related regarding your hearing, completing basic hearing tests (audiometry, middle ear assessment), specific hearing tests related to inner ear (on of the parts of the ear), sitting in sound booth for approximately 10 minutes and writing down any sound you might have heard during or after the period of silence. The entire procedure will take approximately 45 minutes.

All of the information you provide and your tests results will be kept confidential. There will be no risk in participating in this study. However, You can chose to quit at any stage in the process of your participation if you feel any discomfort. You will be given a copy of your test results in basic audiometry tests. You will receive a $10 amazon gift card after the completion of all test procedures. If you chose to withdraw from the study before completion of all the test procedure, you will not get the gift card.

Do you have any questions? If you have any questions later, please contact me at 336-681-0047/ agtayade@uncg.edu or my advisor Dr Tucker at 336-334-5184/datucker@uncg.edu.



APPENDIX H

FACULTY LETTER

Email Script for faculty-Introducing the research to the potential participant

Dear Students,

I am writing to tell you about a study being conducted at the Department of Communication Sciences & Disorder, UNCG by doctoral student Mr. Amitkumar Tayade.

Mr. Tayade is studying *the short-term effects on hearing after a brief period of silence*. He will also examine if these effects can be reduced by delivering a medium shower-like masking sound (for brief period) in the left ear.

I am not a member of his research team, however, I am contacting some of my students to let them know about the research in case they might be interested in learning more.

You may be eligible for this study if you are a male student between the age 18-35 years and if you do not have any history or complaint of ear related disorders (such as hearing loss, constant ringing in the ears. or prolonged history of noise exposure that resulted in hearing loss) or a medical history of neurologic disorders (such as head injury or seizures). Steps for participating in this project;

1. Contact Mr. Tayade via email at agtayade@uncg.edu. He will contact potential subjects to schedule a test time.
2. Every participant will receive a $10 amazon gift card after the completion of all test procedures. Any participant who withdraws from the study before completion of all the test procedure will not get the gift card
3. *Location of test and duration of testing session- 45 minutes*. The testing session will be conducted in the UNCG Speech and Hearing Center, located on the 3rd floor of the Ferguson Building (top floor), room 327-A. Subjects will get a free hearing test to determine their hearing thresholds and for admission to the study.
4. Testing: If your are admitted to the study, you will fill out a short survey about your hearing perceptions during the test after sitting in silence (in a sound booth). Hearing will be measured with Otoacoustic Emissions (OAEs), which measures small sounds in your ear canal.

Your participation in this study is voluntary. Whether or not you participate in this study will have no effect on your grades or relationship with any instructor.

If you are interested in learning more about this research project, please contact Mr. Tayade through email or you may contact him on his cell phone at 336-681-0047.

If you do not wish to receive further communication about this study they can contact Mr. Tayade agtayade@uncg.edu to be remove your name from a contact email list

Thank you for your consideration.

FACULTY NAME

DEPARTMENT